Determination of Drug Pharmacokinetics and Metabolic Profile

Volume II

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David R. Hawkins, Ph.D

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The metabolism and pharmacokinetics of WR 238605 have been studied in beagle dogs after oral and intravenous administration of the carbon-14 labelled drug. Rates and routes of excretion and blood and plasma concentrations of the drug and its metabolites were measured after an intravenous dose of 0.936 mg/kg and after oral doses of 1.7 to 19.5 mg/kg. A similar study was carried out in rhesus monkeys after an oral and intravenous dose of 0.936 mg/kg.

The bioavailability and pharmacokinetics of pyridostigmine have been studied in beagle dogs after intravenous doses and oral administration of different formulations including a syrup and extended-release tablets.

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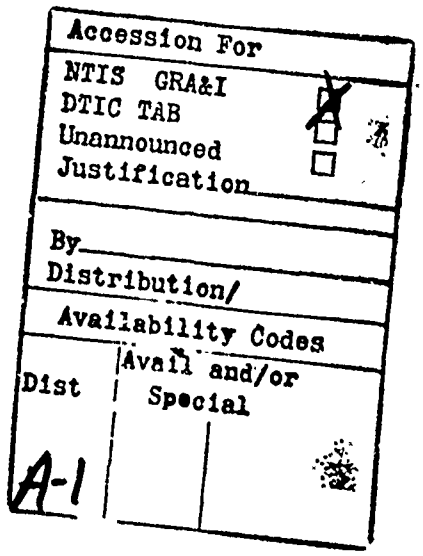
FOREWORD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).



CONTENTS

METABOLISM AND PHARMACOKINETICS OF

^{14}C-WR 238605 IN BEAGLE DOGS

SUMMARY

1. The purpose of this study was to carry out a pilot investigation of the metabolism and pharmacokinetics in the beagle dog, of the compound ^{14}C-WR 238605 succinate, a new anti-malarial drug. ^{14}C-WR 238605 succinate was administered orally, as a suspension in 1% aqueous carboxymethylcellulose solution and by intravenous injection as a solution in physiological saline to two dogs at a dose level of 5 mg/kg.

2. Excretion of radioactivity after oral and intravenous administration of ^{14}C-WR 238605 succinate was very similar.

Excretion of radioactivity in the faeces and urine accounted for approximately 45% and 15% respectively of the administered dose after 10 days.

Excretion of radioactivity was very slow, and only approximately 60% of the dose was recovered in the excreta after 10 days. These results indicated that oral doses at this level were quantitatively absorbed.

3. Mean plasma concentrations of radioactivity following oral and intravenous administrations were also very similar. Peak levels of approximately 0.7 µg equivalents of WR 238605 free base/ml were achieved after 48-72 hours. Plasma concentration of radioactivity then declined with half-lives of approximately 182 hours. Radioactivity was still detected in plasma 5 weeks after dosing when the mean concentration was approximately 0.04 µg/ml.

4. Mean concentrations of radioactivity in whole-blood were also very similar following oral and intravenous administration and initially similar to those in plasma. However, the mean peak levels, approximately 2.3 µg/ml, were about three-fold higher than those in plasma and after 5 weeks the mean concentrations of radioactivity in whole-blood, approximately 0.23 µg/ml, were five-fold higher than those in plasma. Assuming a packed cell volume of 40% the cells therefore, contained concentrations 5 to 10 fold higher than plasma.

5. Mean plasma concentrations of WR 238605 increased from approximately 0.03 µg/ml 30 mins after oral and intravenous administration to reach peak levels, after 4 hours of approximately 0.1 µg/ml and 0.05 µg/ml respectively. The proportions of the total plasma radioactivity accounted for by WR 238605 decreased from approximately 40% at the first sample time to less than 5% after 72 hours.

6. Very little WR 238605 was excreted unchanged in the urine the major metabolite, representing at least 50% of the urinary radioactivity, being a chromatographically less polar component. This compound was also a major component in plasma (7-hour sample) and faeces (0-24 hour sample) where it accounted for approximately 50% and 30% of the radioactivity respectively.

   Both WR 238605 and its metabolites were found to be almost completely bound to plasma protein.

TABLE 1

Excretion of radioactivity by beagle dogs after single oral and intravenous doses (5 mg/kg) of ^{14}C-WR 238605 succinate

Results are expressed as % administered radioactivity

Sample	Time (hours)	Oral			Intravenous		
		Dog 5	Dog 6	Mean	Dog 5	Dog 6	Mean
Faeces	0- 24	16.23	15.16	15.70	4.86	7.08	5.97
	24- 48	8.00	6.88	7.44	6.72	9.83	8.28
	48- 72	4.49	4.75	4.62	7.22	6.71	6.97
	72- 96	4.11	4.91	4.51	4.59	6.05	5.32
	96-120	3.37	3.90	3.64	3.19	2.64	2.92
	120-144	3.06	3.08	3.07	3.18	4.68	3.93
	144-168	2.67	2.58	2.63	3.70	2.37	3.04
	168-192	2.37	2.96	2.67	2.52	3.55	3.04
	192-216	1.83	1.70	1.77	2.01	1.58	1.80
	216-240	1.53	1.08	1.31	1.56	1.79	1.68
	Total	47.66	47.00	47.33	39.55	46.28	42.92
Urine	0- 6	0.31	0.40	0.36	0.41	0.67	0.54
	6- 24	1.63	2.07	1.85	1.52	2.06	1.79
	24- 48	1.84	2.23	2.04	1.88	2.66	2.27
	48- 72	1.68	2.15	1.92	1.68	2.22	1.95
	72- 96	1.56	2.10	1.83	1.33	1.83	1.58
	96-120	1.50	1.93	1.72	1.15	1.78	1.47
	120-144	1.31	1.58	1.45	1.21	1.53	1.37
	144-168	1.24	1.41	1.33	1.06	1.39	1.23
	168-192	1.08	1.22	1.15	0.99	1.19	1.09
	192-216	0.91	1.04	0.98	1.17	0.85	1.01
	216-240	0.83	0.91	0.87	0.82	0.89	0.86
	Total	13.89	17.04	15.47	13.22	17.07	15.15
Cage wash	0- 24	0.31	0.26		0.12	0.18	
	24- 48	0.27	0.22		0.12	0.13	
	48- 72	0.14	0.19		0.11	0.19	
	72- 96	0.13	0.15		0.10	0.17	
	96-120	0.13	0.16		0.15	0.14	
	120-144	0.12	0.13		0.09	0.10	
	144-168	0.13	0.11		0.07	0.09	
	168-192	0.08	0.11		0.07	0.10	
	192-216	0.10	0.10		0.06	0.07	
	216-240	0.08	0.07		0.05	0.10	
	Total	1.49	1.50		0.94	1.27	
Overall total		63.04	65.54		53.71	64.62	

TABLE 2

Cumulative excretion of radioactivity by beagle dogs after oral and intravenous doses (5 mg/kg) of ^{14}C-WR 238605 succinate

Results are expressed as % administered radioactivity

Sample	Time (hours)	Oral			Intravenous		
		Dog 5	Dog 6	Mean	Dog 5	Dog 6	Mean
Faeces	0- 24	16.23	15.16	15.70	4.86	7.08	5.97
	0- 48	24.23	22.04	23.14	11.58	16.91	14.25
	0- 72	28.72	26.79	27.76	18.80	23.62	21.21
	0- 96	32.83	31.70	32.27	23.39	29.67	26.53
	0-120	36.20	35.60	35.90	26.58	32.31	29.45
	0-144	39.26	38.68	38.97	29.76	36.99	33.38
	0-168	41.93	41.26	41.60	33.46	39.36	36.41
	0-192	44.30	44.22	44.26	35.98	42.91	39.45
	0-216	46.13	45.92	46.03	37.99	44.49	41.24
	0-240	47.66	47.00	47.33	39.55	46.28	42.92
Urine	0- 6	0.31	0.40	0.36	0.41	0.67	0.54
	0- 24	1.94	2.47	2.21	1.93	2.73	2.33
	0- 48	3.78	4.70	4.24	3.81	5.39	4.60
	0- 72	5.46	6.85	6.16	5.49	7.61	6.55
	0- 96	7.02	8.95	7.99	6.82	9.44	8.13
	0-120	8.52	10.88	9.70	7.97	11.22	9.60
	0-144	9.83	12.46	11.15	9.18	12.75	10.97
	0-168	11.07	13.87	12.47	10.24	14.14	12.19
	0-192	12.15	15.09	13.62	11.23	15.33	13.28
	0-216	13.06	16.13	14.60	12.40	16.18	14.29
	0-240	13.89	17.04	15.47	13.22	17.07	15.15
Cage wash	0- 24	0.31	0.26		0.12	0.18	
	0- 48	0.58	0.48		0.24	0.31	
	0- 72	0.72	0.67		0.35	0.50	
	0- 96	0.85	0.82		0.45	0.67	
	0-120	0.98	0.98		0.60	0.81	
	0-144	1.10	1.11		0.69	0.91	
	0-168	1.23	1.22		0.76	1.00	
	0-192	1.31	1.33		0.83	1.10	
	0-216	1.41	1.43		0.89	1.17	
	0-240	1.49	1.50		0.94	1.27	
Overall total		63.04	65.54		53.71	64.62	

TABLE 3

Concentrations of radioactivity in plasma of dogs after single oral and intravenous doses of ^{14}C-WR 238605 succinate (5 mg/kg)

Results are expressed as µg equivalents of WR 238605 free base/ml

Time (hours)	Oral			Intravenous		
	Animal no.			Animal no.		
	5	6	Mean	5	6	Mean
0.08	NS	NS	NS	0.790	0.985	0.888
0.25	NS	NS	NS	0.403	0.451	0.427
0.5	0.048	0.052	0.050	0.336	0.366	0.351
0.75	NS	NS	NS	0.307	0.339	0.323
1	0.083	0.137	0.110	0.294	0.326	0.310
2	0.128	0.193	0.161	0.295	0.323	0.309
3	0.169	0.258	0.214	0.332	0.378	0.355
4	0.200	0.353	0.277	0.337	0.415	0.376
5	0.238	0.389	0.314	0.347	0.457	0.402
7	0.318	0.536	0.427	0.373	0.516	0.445
12	0.393	0.649	0.521	0.373	0.578	0.476
24	0.440	0.749	0.595	0.399	0.688	0.544
30	0.496	0.816	0.656	0.449	0.758	0.604
48	0.495	0.879	0.687	0.443	0.711	0.577
72	0.489	0.844	0.667	0.489	0.849	0.669
96	0.481	0.858	0.670	0.444	0.817	0.631
120	0.472	0.805	0.639	0.419	0.777	0.598
144	0.432	0.742	0.587	0.403	0.686	0.545
168	0.371	0.618	0.495	0.406	0.701	0.554
192	0.344	0.577	0.461	0.347	0.594	0.471
216	0.333	0.518	0.426	0.322	0.545	0.434
240	0.292	0.449	0.371	0.284	0.497	0.391
336	0.197	0.316	0.257	0.195	0.339	0.267
504	0.112	0.161	0.137	0.104	0.158	0.131
672	0.054	0.073	0.064	0.058	0.087	0.073
840	0.034	0.047	0.041	0.033	0.052	0.043

NS No sample

TABLE 4

Concentrations of radioactivity in whole-blood of dogs after single oral and intravenous doses of ^{14}C-WR 238605 succinate (5 mg/kg)

Results are expressed as µg equivalents of WR 238605 free base/ml

Time (hours)	Oral			Intravenous		
	Animal no.			Animal no.		
	5	6	Mean	5	6	Mean
0.08	NS	NS	-	0.888	1.02	0.954
0.25	NS	NS	-	0.458	0.488	0.473
0.5	0.050	0.043	0.047	0.344	0.362	0.353
0.75	NS	NS	-	0.336	0.347	0.342
1	0.080	0.108	0.094	0.340	0.368	0.354
2	0.138	0.164	0.151	0.331	0.362	0.347
3	0.179	0.235	0.207	0.387	0.399	0.393
4	0.230	0.321	0.276	0.410	0.441	0.426
5	0.301	0.416	0.359	0.418	0.496	0.457
7	0.386	0.574	0.480	0.481	0.633	0.557
12	0.622	1.06	0.841	0.577	0.885	0.731
24	0.879	1.41	1.14	0.702	1.32	1.01
30	1.08	1.91	1.50	0.869	1.49	1.18
48	1.24	1.75	1.50	1.15	1.86	1.51
72	1.52	2.49	2.01	1.61	2.10	1.86
96	1.70	2.81	2.26	1.67	2.34	2.01
120	1.81	2.57	2.19	1.69	2.78	2.24
144	1.73	2.53	2.13	1.67	2.63	2.15
168	1.58	2.27	1.93	1.76	2.79	2.28
192	1.41	1.77	1.59	1.49	2.33	1.91
216	1.32	1.47	1.40	1.44	2.22	1.83
240	1.21	1.12	1.17	1.29	1.88	1.59
336	0.780	1.11	0.945	0.791	1.36	1.08
504	0.447	0.608	0.528	0.408	0.700	0.554
672	0.299	0.478	0.389	0.233	0.405	0.319
840	0.181	0.316	0.249	0.150	0.268	0.209

NS No sample

TABLE 5

Concentrations of WR 238605 in plasma of dogs after single oral and intravenous doses of ^{14}C-WR 238605 succinate (5 mg/kg)

Results are expressed as µg of WR 238605 free base/ml

Time (hours)	Oral			Intravenous		
	Animal no.			Animal no.		
	5	6	Mean	5	6	Mean
0.08	NS	NS	NS	0.238	0.230	0.234
0.25	NS	NS	NS	0.056	0.050	0.053
0.5	0.029	0.026	0.028	0.034	0.028	0.031
0.75	NS	NS	NS	0.029	0.028	0.029
1	0.034	0.038	0.036	0.017	0.030	0.024
2	0.051	0.032	0.042	0.022	0.022	0.022
3	0.061	0.083	0.072	0.021	0.031	0.026
4	0.065	0.142	0.104	0.057	0.034	0.046
5	0.079	0.071	0.075	0.015	0.022	0.019
7	0.065	0.079	0.072	0.060	0.026	0.043
12	0.105	0.065	0.085	0.059	0.027	0.043
24	0.062	0.113	0.088	0.034	0.040	0.037
30	0.074	0.106	0.090	0.025	0.033	0.029
48	0.043	0.022	0.033	0.021	0.024	0.023
72	0.036	0.018	0.027	0.021	<0.015	

NS No sample

TABLE 6

Pharmacokinetic parameters for the decline in concentrations of radioactivity with time in plasma and whole-blood of dogs after single oral and intravenous doses of ^{14}C-WR 238605 succinate (5 mg/kg)

	Half-life* (hours)			Area under curve/ (µg hrs/ml)		
	Dog 5	Dog 6	Mean	Dog 5	Dog 6	Mean
Plasma (oral)	188.7	174.5	181.6	170.1	274.9	222.5
Whole-blood (oral)	214.5	260.9	237.7	636.4	889.4	762.9
Plasma (i.v.)	187.2	177.3	182.3	165.5	278.7	222.1
Whole-blood (i.v.)	185.2	197.6	191.4	623.8	994.2	809.0

*$t_{\frac{1}{2}}$ measured between 168 hours and 840 hours
/ A.U.C. measured up to 840 hours

TABLE 7

Degree of plasma protein binding of ^{14}C-WR 238605 and metabolites following single oral and intravenous doses of ^{14}C-WR 238605 succinate to dogs (5 mg/kg)

Intravenous administration

Pooled plasma sample number	Plasma sample contained in pool (hours)		Degree of plasma protein binding of radioactivity (%; duplicate measurements)	Mean
	Dog 5	Dog 6		
1	0.08-0.75	-	99.4 99.4	99.4
2	48-120	-	97.6 97.8	97.7
3	-	0.08-0.75	99.1 99.3	99.2
4	-	48-120	98.2 98.1	98.2

Oral administration

5	48-120	-	96.5 97.8	97.2
6	-	48-120	97.9 97.7	97.8
7≠	-	-	94.3 96.3 96.1 97.5 97.2	96.3

≠ Sample 7 was prepared by spiking control dog plasma with ^{14}C-WR 238605 succinate (approximately 2 µg/ml, 5 replicate measurements)

TABLE 8

The recovery of ^{14}C-WR 238605 from control dog plasma to which it had been added at concentrations of 21 ng/ml to 2122 ng/ml

Concentration of ^{14}C-WR 238605 succinate (ng/ml)	Recovery of radioactivity in* the WR 238605 hplc fraction
21	118.8
106	86.3
531	105.9
2122	78.9

* Mean of two experiments

FIGURE 1

The mean cumulative excretion of radioactivity in the urine and faeces of dogs 5 and 6 following oral administration of single doses of ^{14}C-WR 238605 succinate (5 mg/kg)

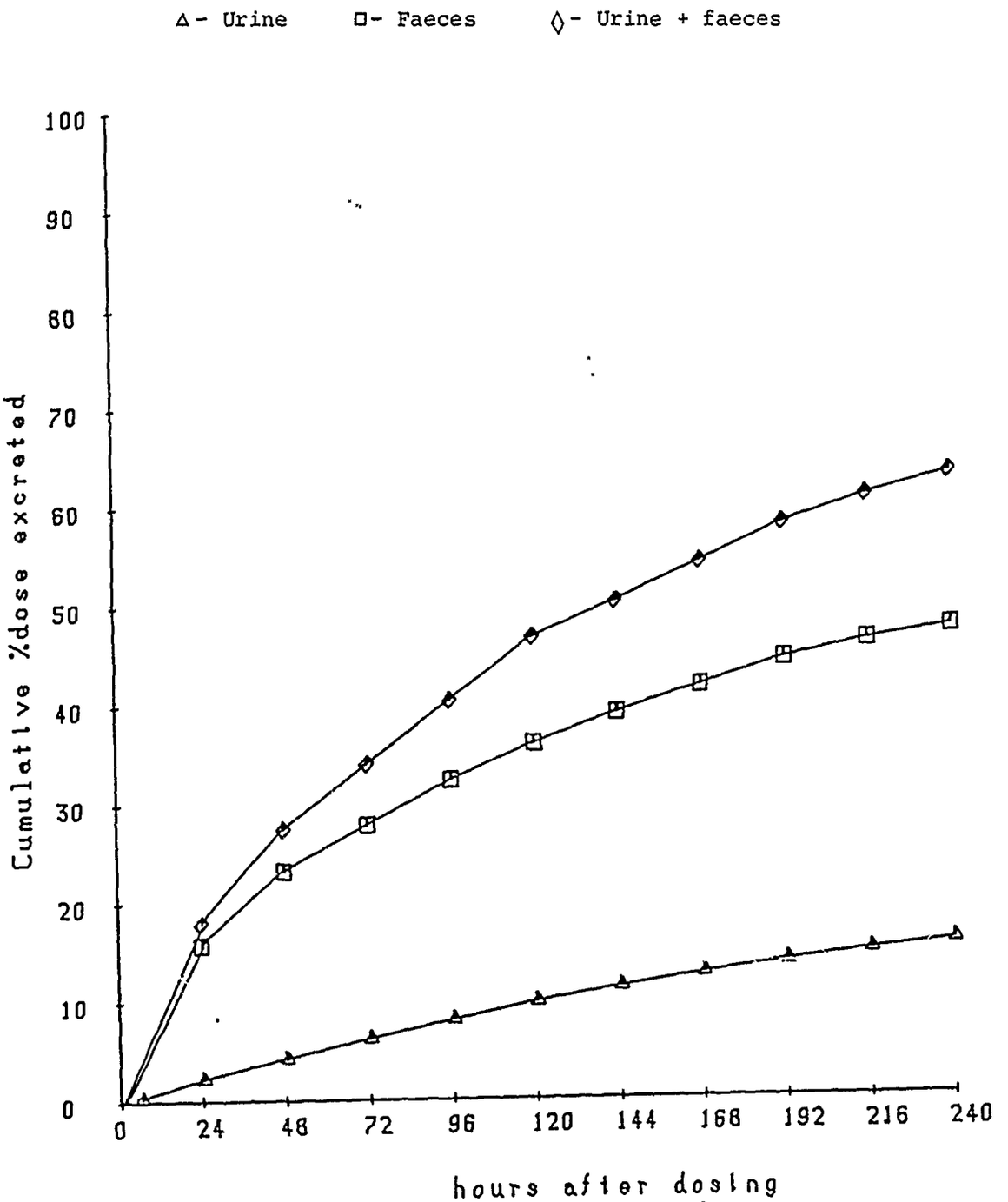


FIGURE 2

The mean cumulative excretion of radioactivity in the urine and faeces of dogs 5 and 6 following intravenous administration of single doses of ^{14}C-WR 238605 succinate (5 mg/kg)

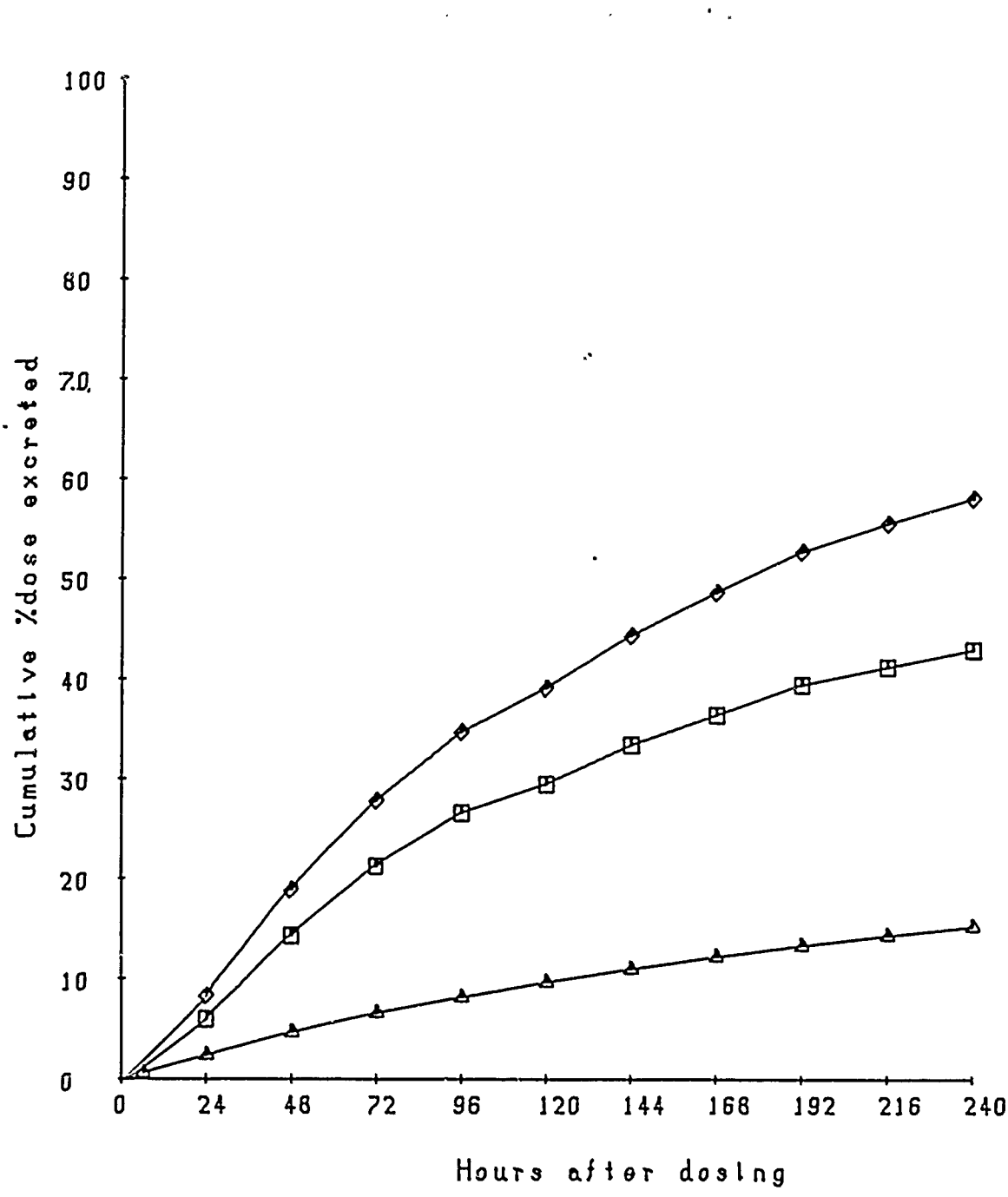


FIGURE 3

The mean rates of excretion of radioactivity in the urine of dogs 5 and 6 following oral (▲) and intravenous (■) administration of ^{14}C-WR 238605 (5 mg/kg)

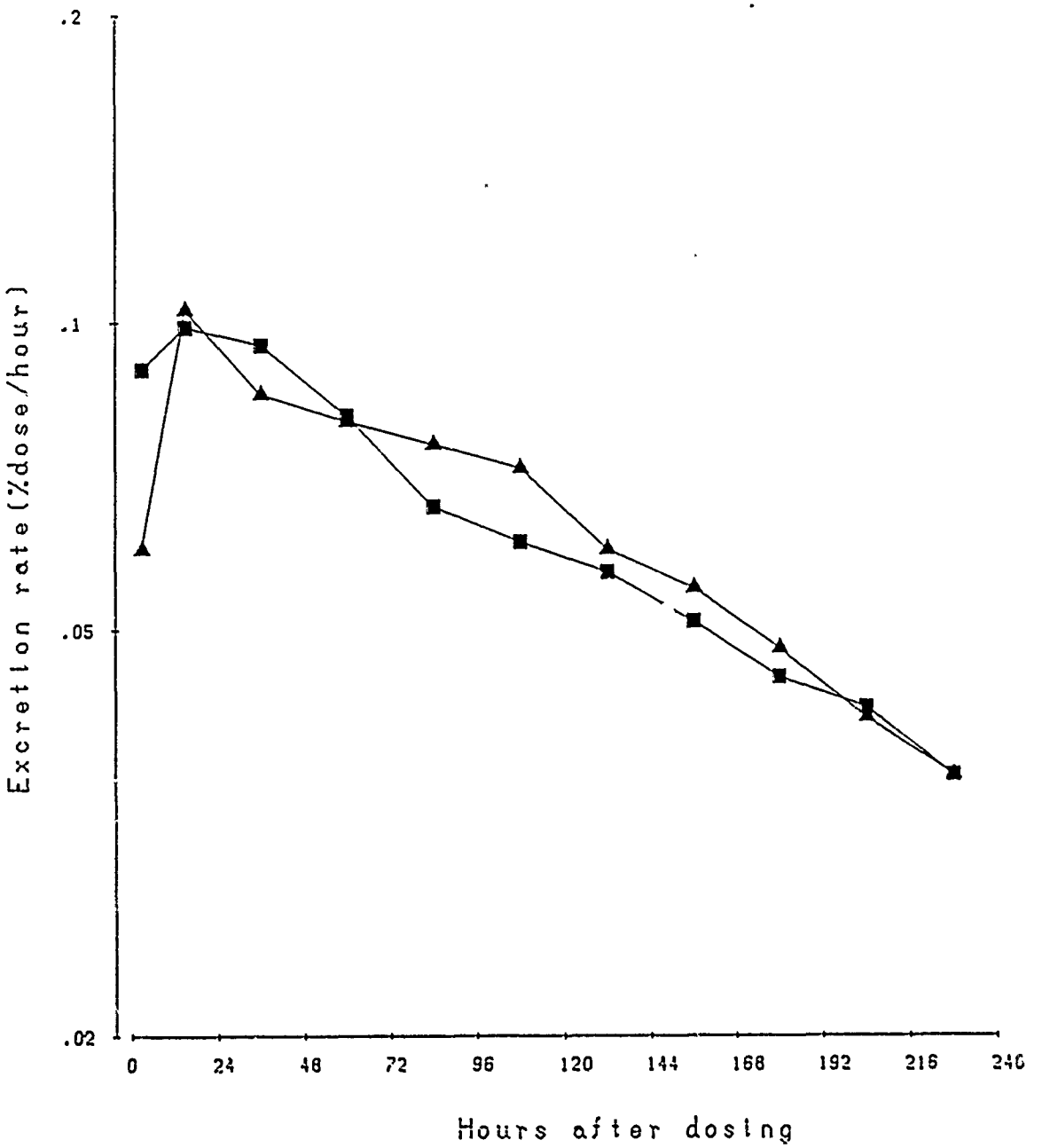


FIGURE 4

Concentrations of total radioactivity in plasma and whole-blood of dogs following single oral doses of ^{14}C-WR 238605 succinate (5 mg/kg) (values before 30 hours not shown)

♦- dog 5 plasma ▲- dog 6 plasma ◊-5 whole-blood △-6 whole-blood

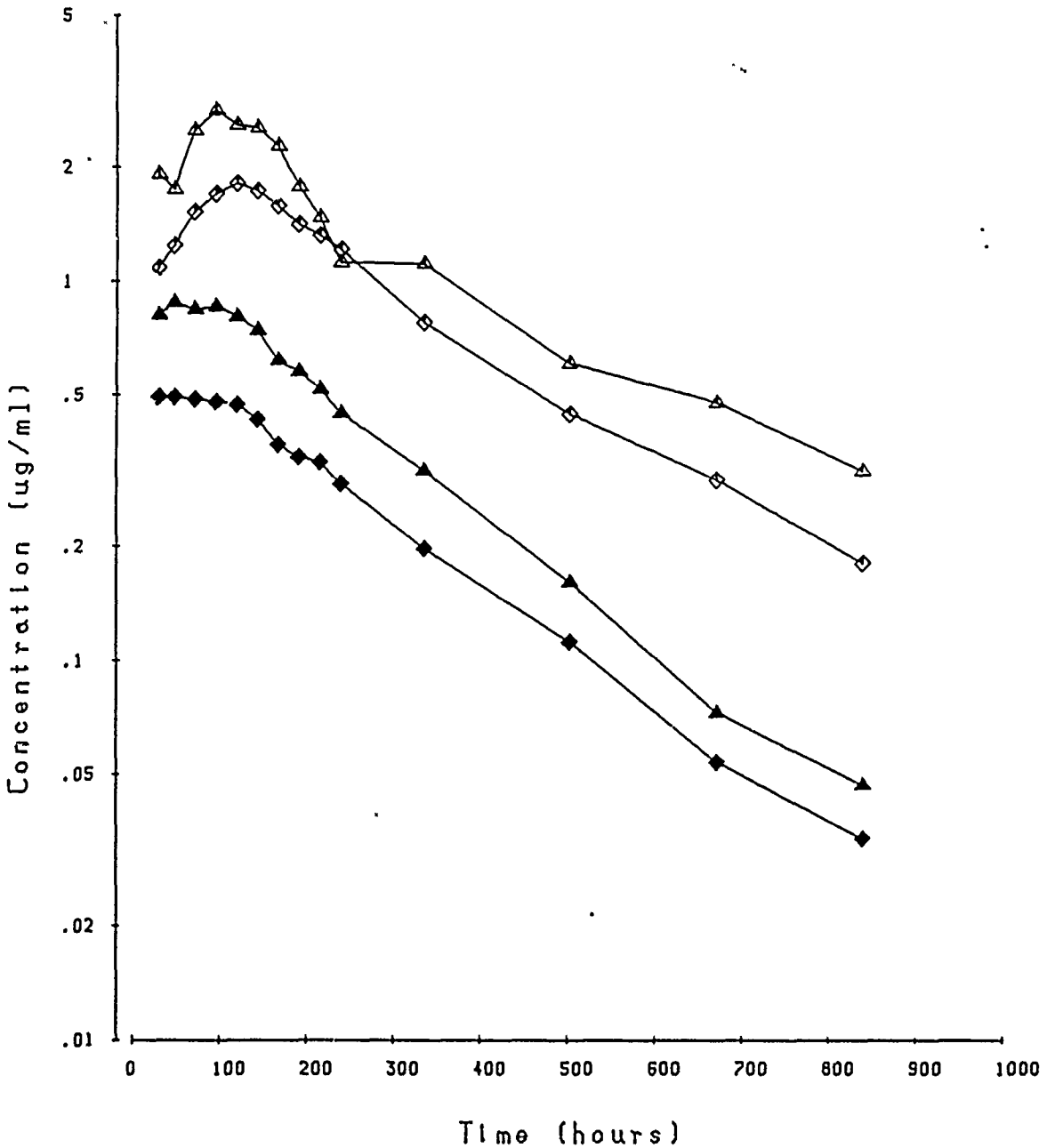


FIGURE 5

Concentrations of total radioactivity in plasma and whole-blood of dogs following single intravenous doses of ^{14}C-WR 238605 succinate (5 mg/kg)
(values before 30 hours not shown)

♦- dog 5 plasma ▲- dog 6 plasma ◊-5 whole-blood △-6 whole-blood

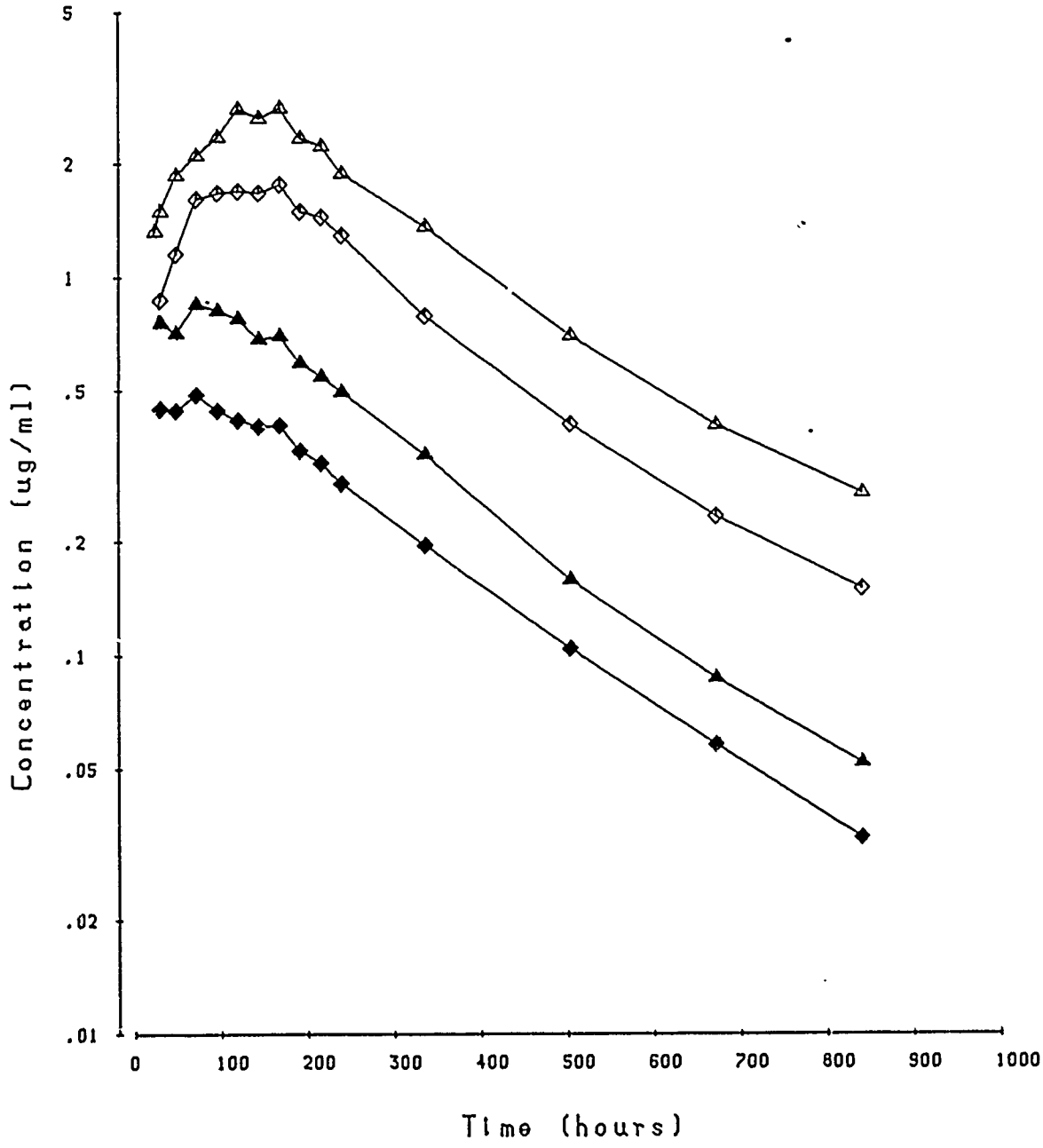


FIGURE 6

Mean concentrations of total radioactivity in plasma and whole-blood of dogs following single oral and intravenous doses of ^{14}C-WR 238605 succinate (5 mg/kg)
(values before 30 hours not shown)

▲-mean oral plasma concentration ◆-mean intravenous plasma concentration
◇-mean oral whole-blood concentration △-mean intravenous whole-blood concentration

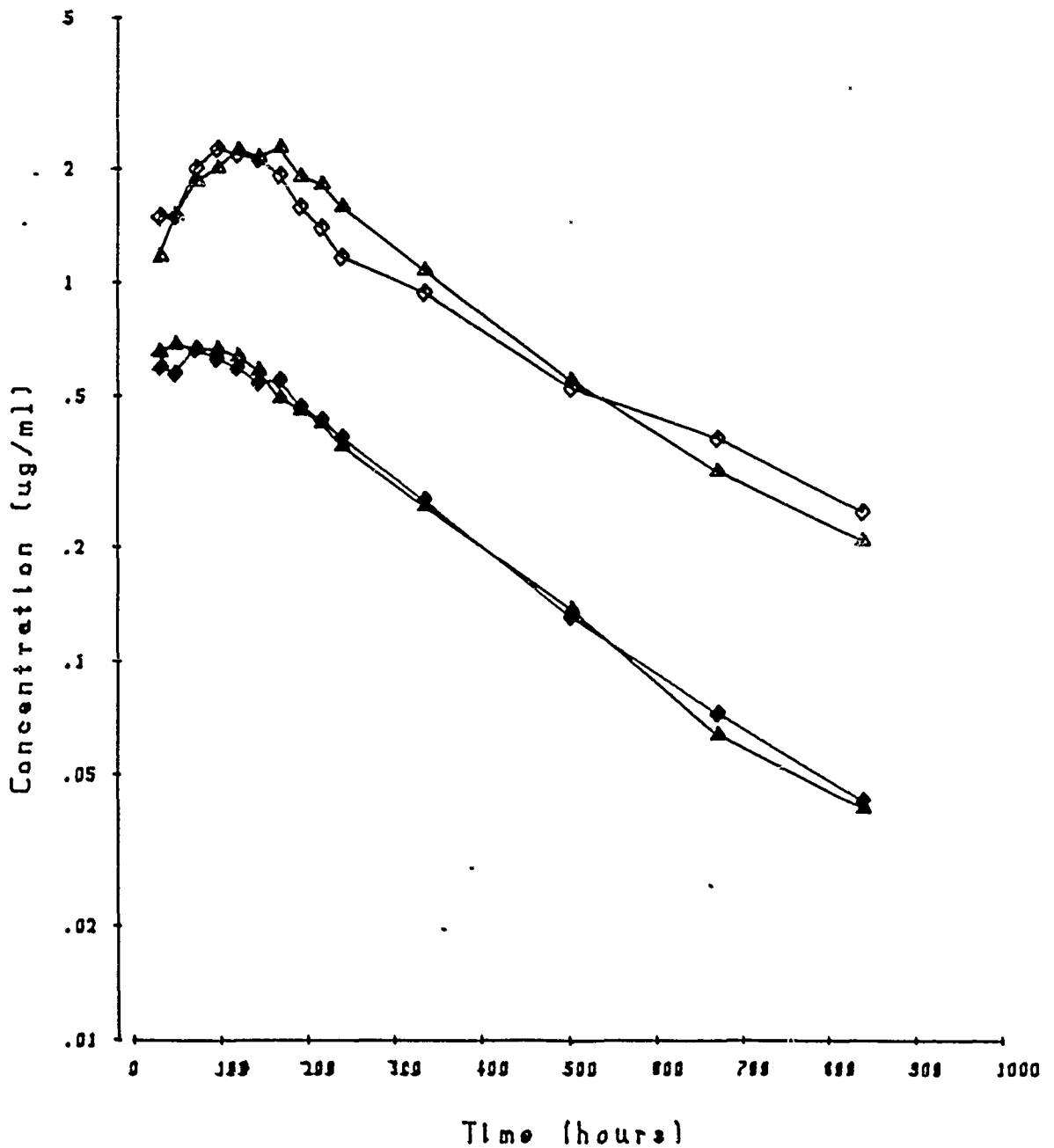


FIGURE 7

Concentrations of total radioactivity in whole-blood (Δ) and plasma (◇) and of WR 238605 in plasma (◆) of dog 5 following a single oral dose of ^{14}C-WR 238605 succinate (5 mg/kg)

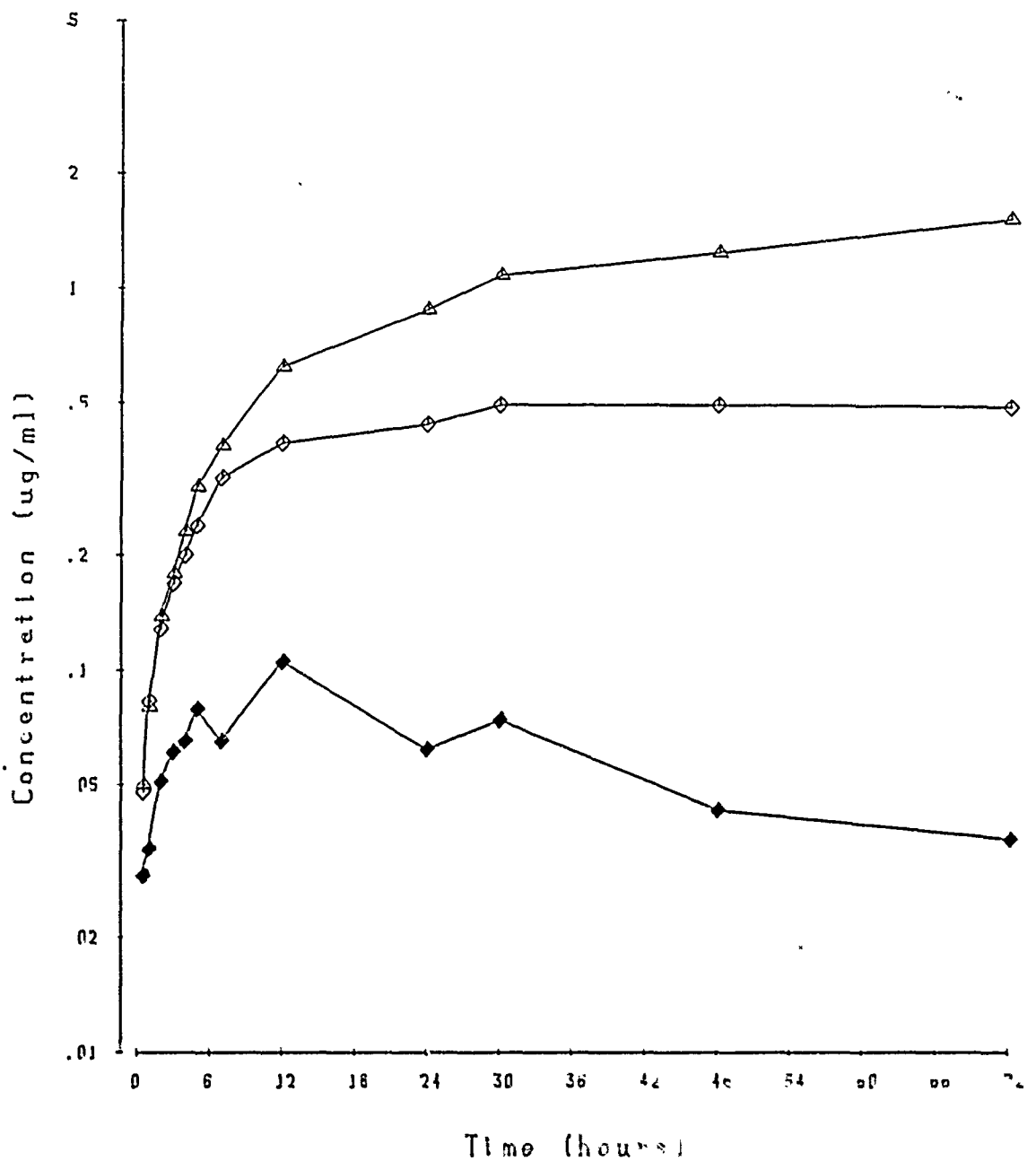


FIGURE 8

Concentrations of total radioactivity in whole-blood (Δ) and plasma (◇) and of WR 238605 in plasma (◆) of dog 6 following a single oral dose of ^{14}C-WR 238605 succinate (5 mg/kg)

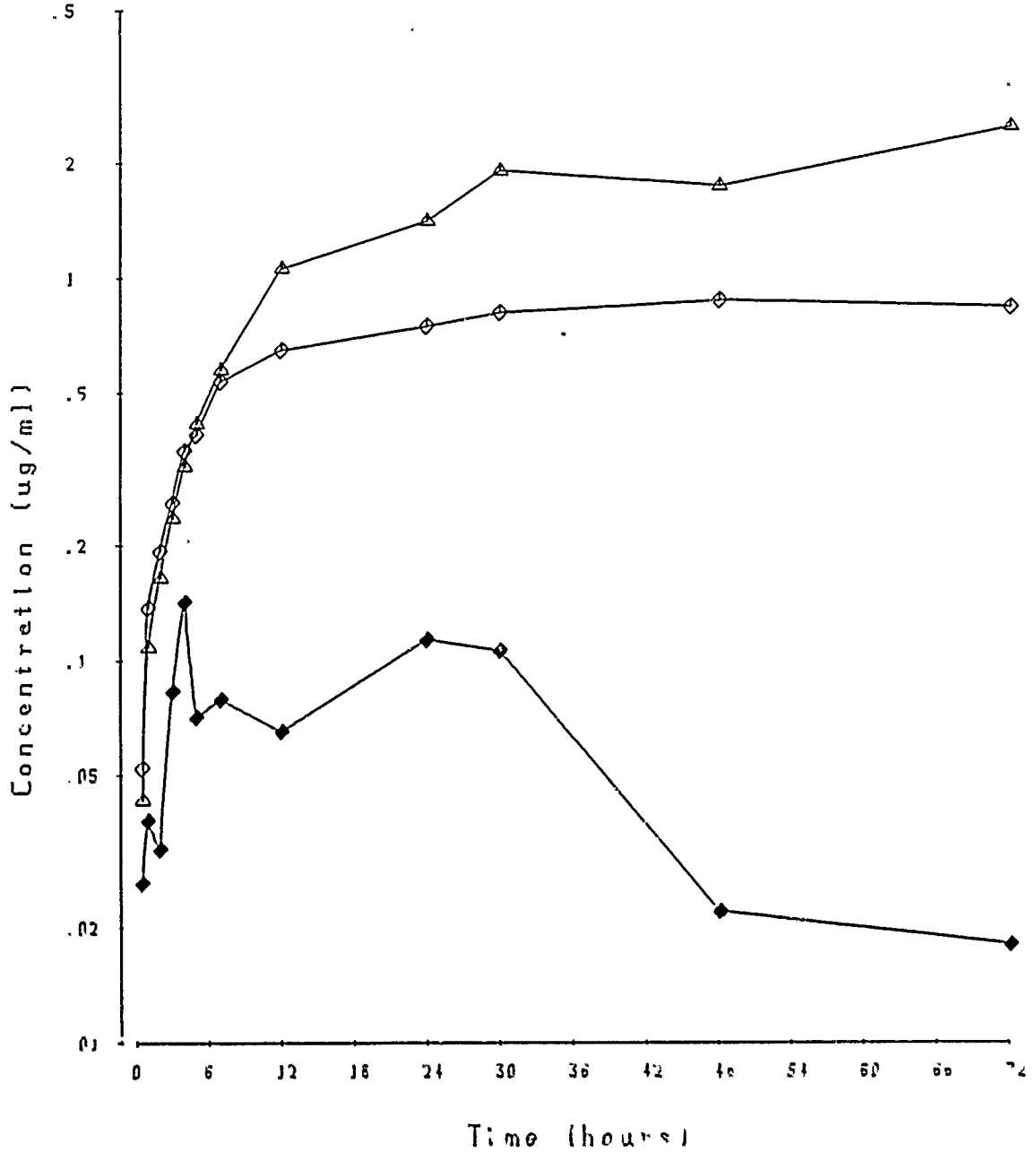


FIGURE 9

Mean concentrations of total radioactivity in whole-blood (△) and plasma (◇) and of WR 238605 in plasma (◆) of dogs following a single oral dose of ^{14}C-WR 238605 succinate (5 mg/kg)

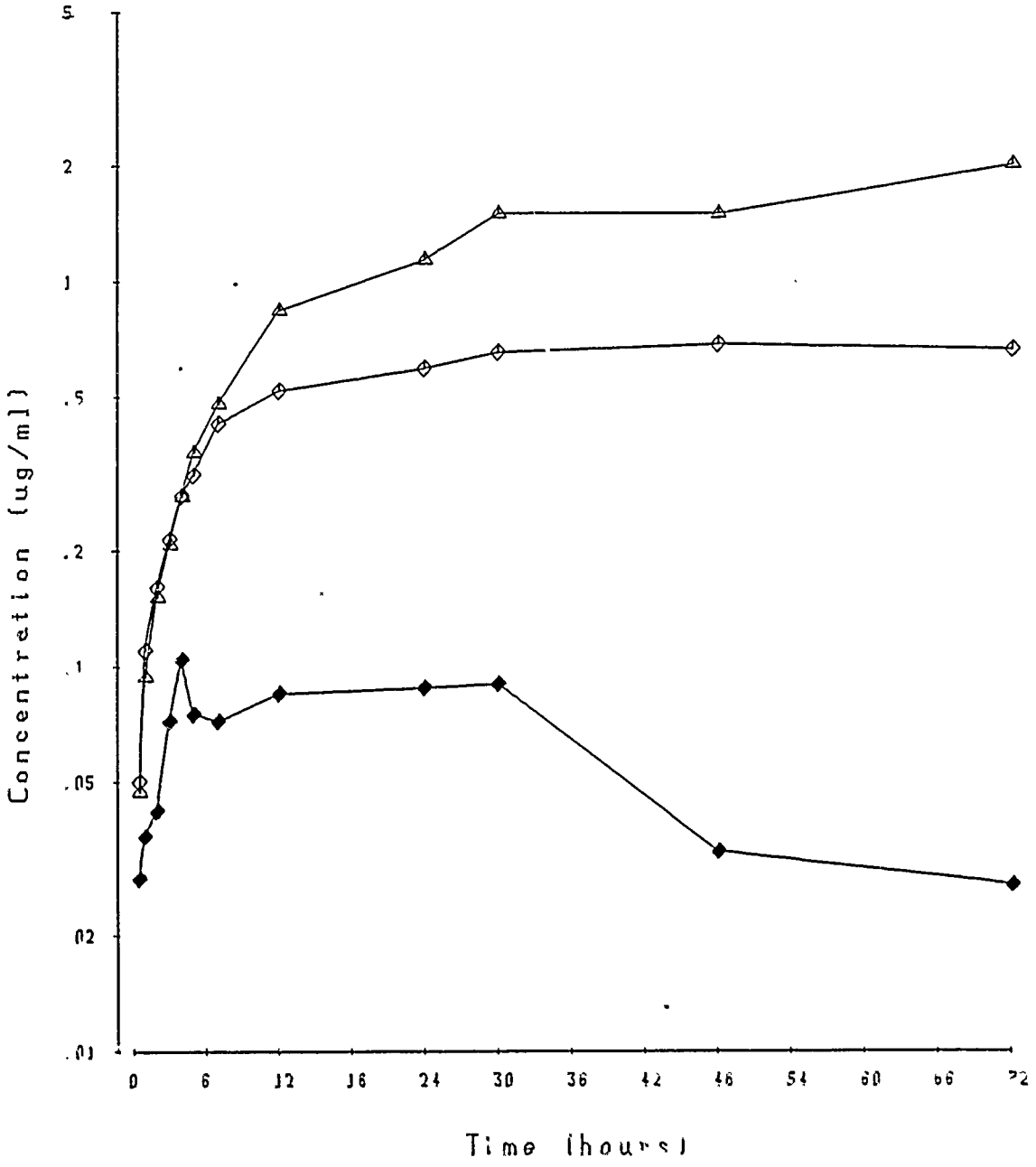


FIGURE 10

Concentrations of total radioactivity in plasma (◇) and whole-blood (△) and of WR 238605 in plasma (◆) of dog 5 following a single i.v. dose of ^{14}C-WR 238605 succinate (5 mg/kg)

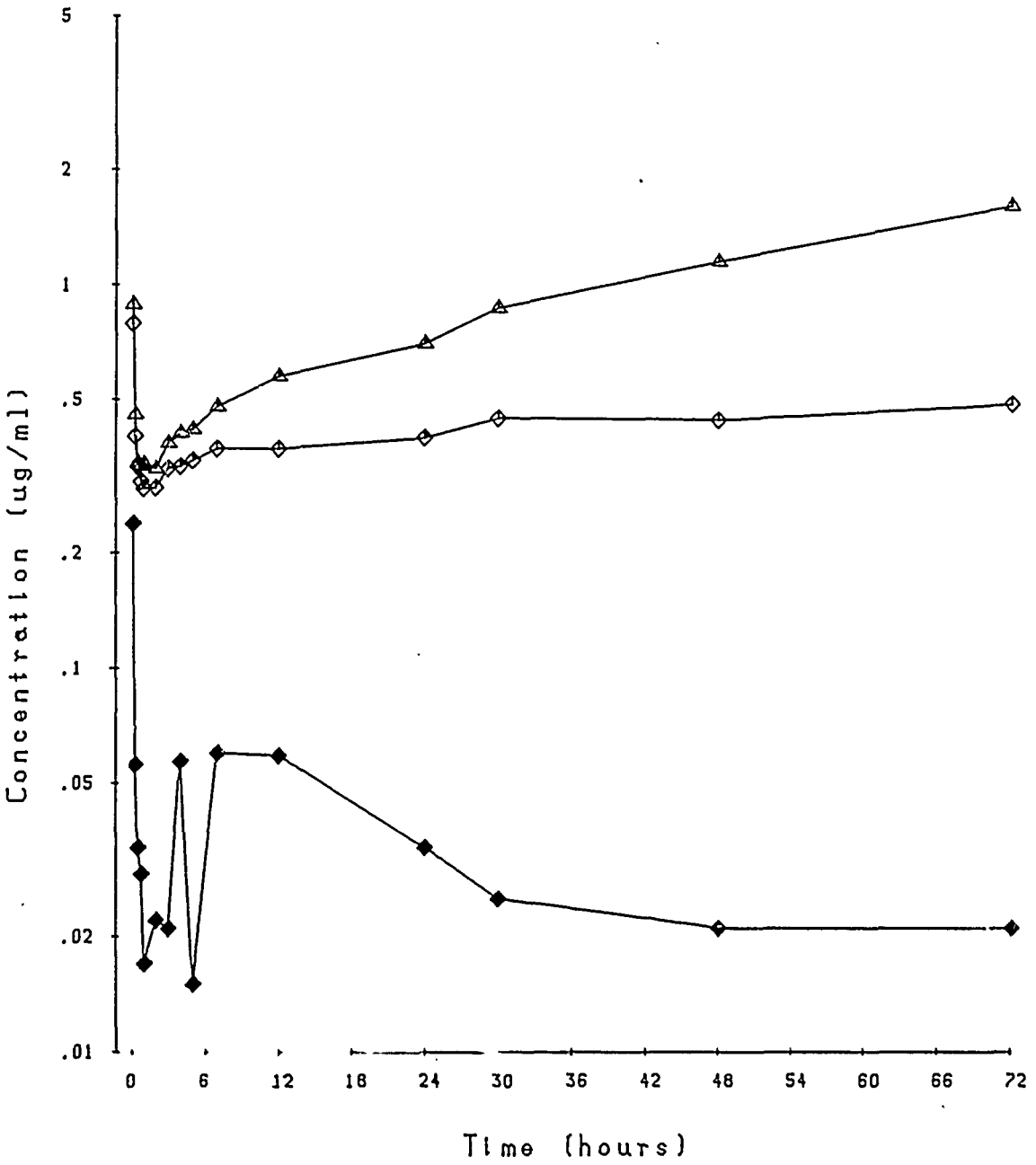


FIGURE 11

Concentrations of total radioactivity in plasma (◇) and whole-blood (△) and of WR 238605 in plasma (◆) of dog 6 following a single i.v. dose of ^{14}C-WR 238605 succinate (5 mg/kg)

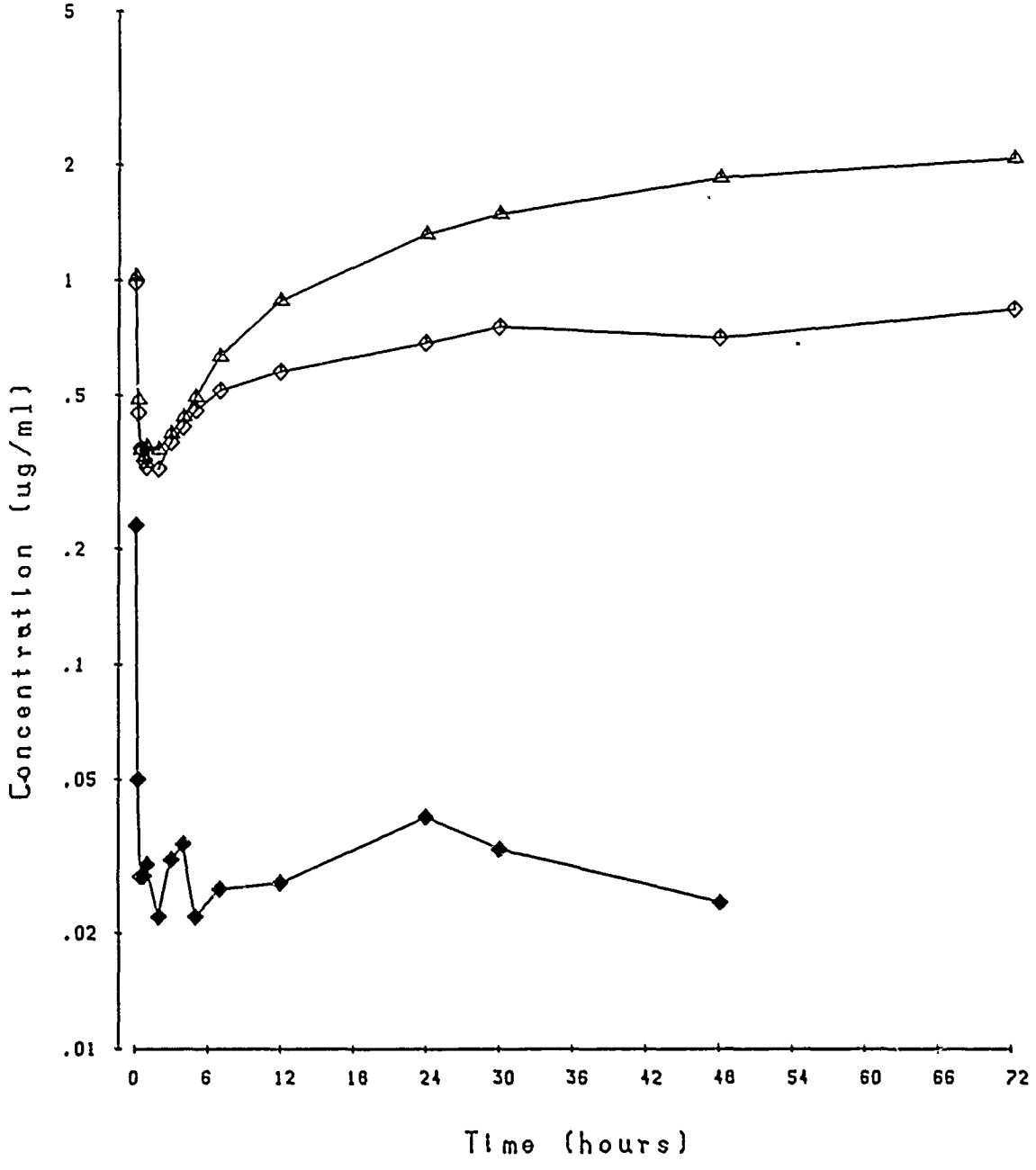


FIGURE 12

Mean concentrations of total radioactivity in whole-blood (Δ) and plasma (◇) and of WR 238605 in plasma (◆) of dogs following a single intravenous dose of ^{14}C-WR 238605 succinate (5 mg/kg)

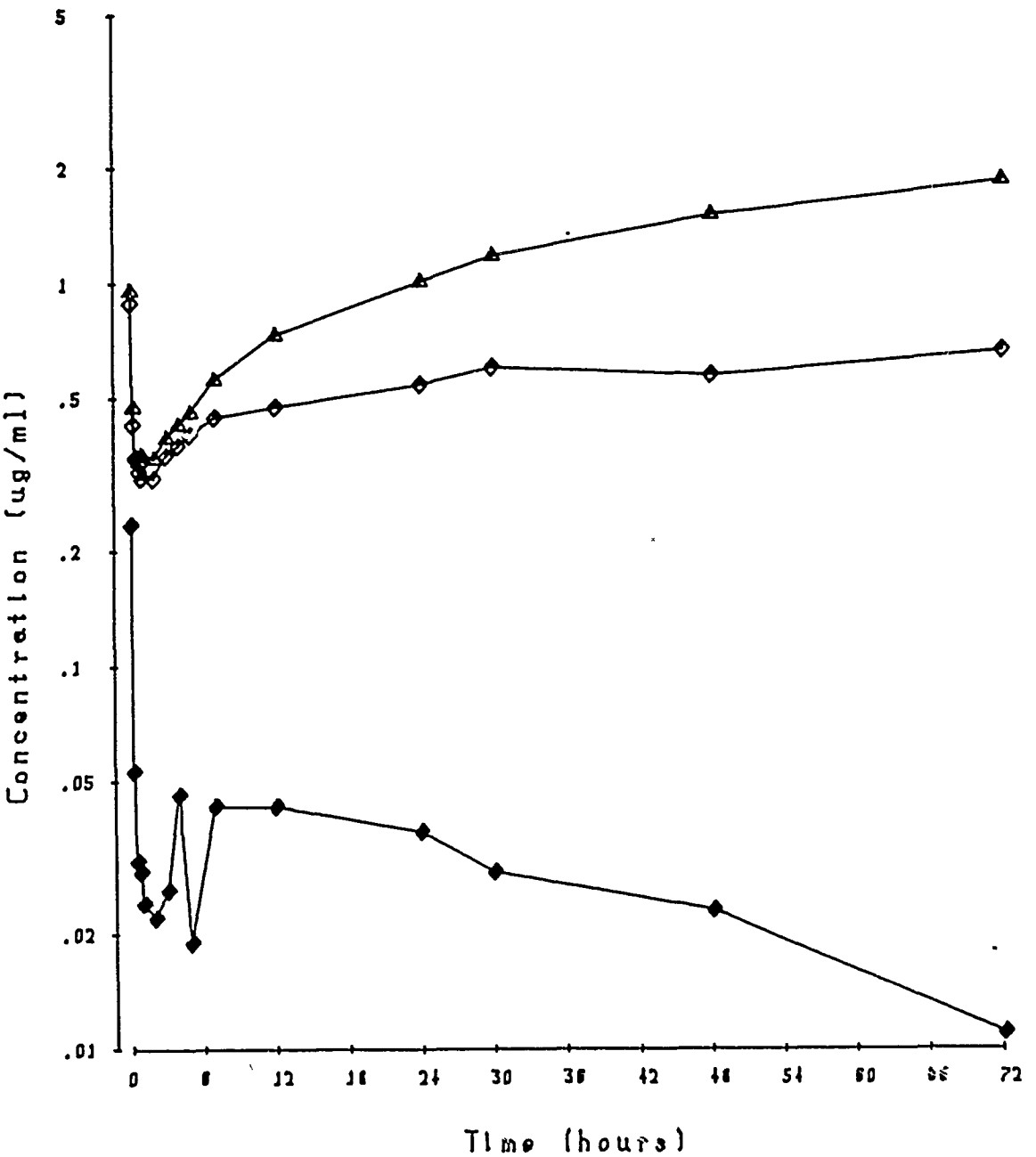
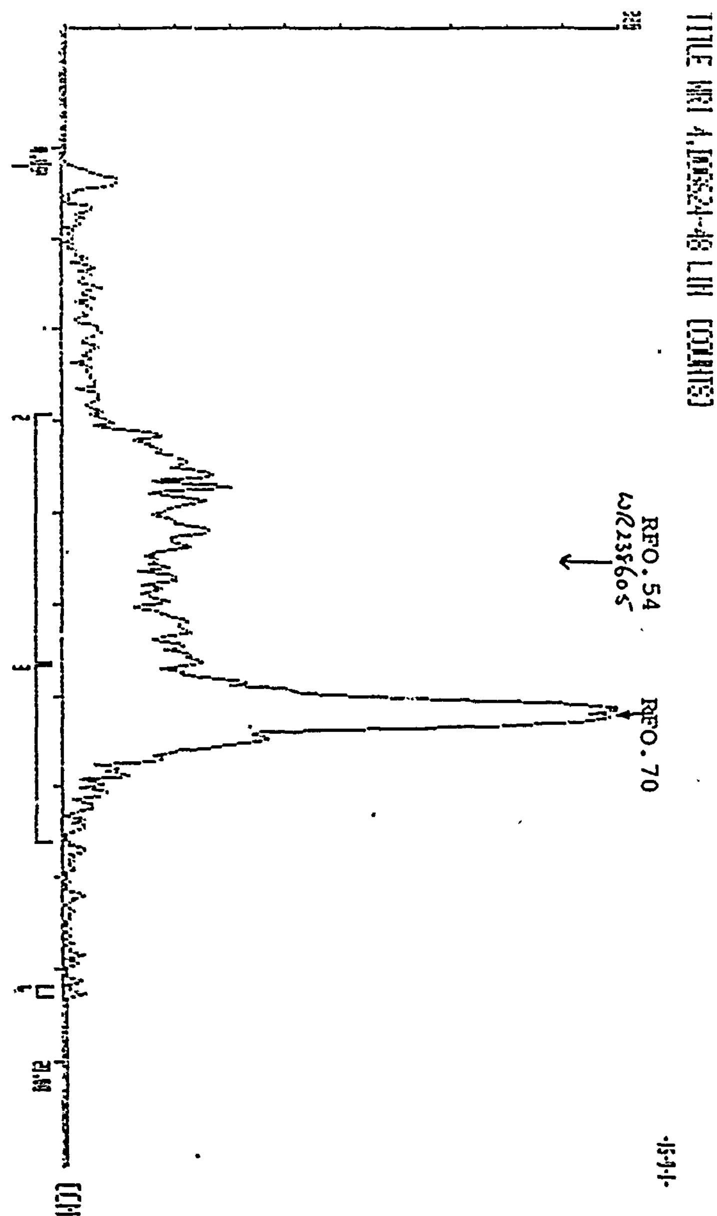


FIGURE 13

Thin-layer radiochromatogram of a methanol extract of dog urine (24-48 hr sample) following oral administration of ^{14}C-WR 238605 succinate (5 mg/kg). Developing solvent was methanol : 35% aqueous ammonia (25 : 1 v/v)

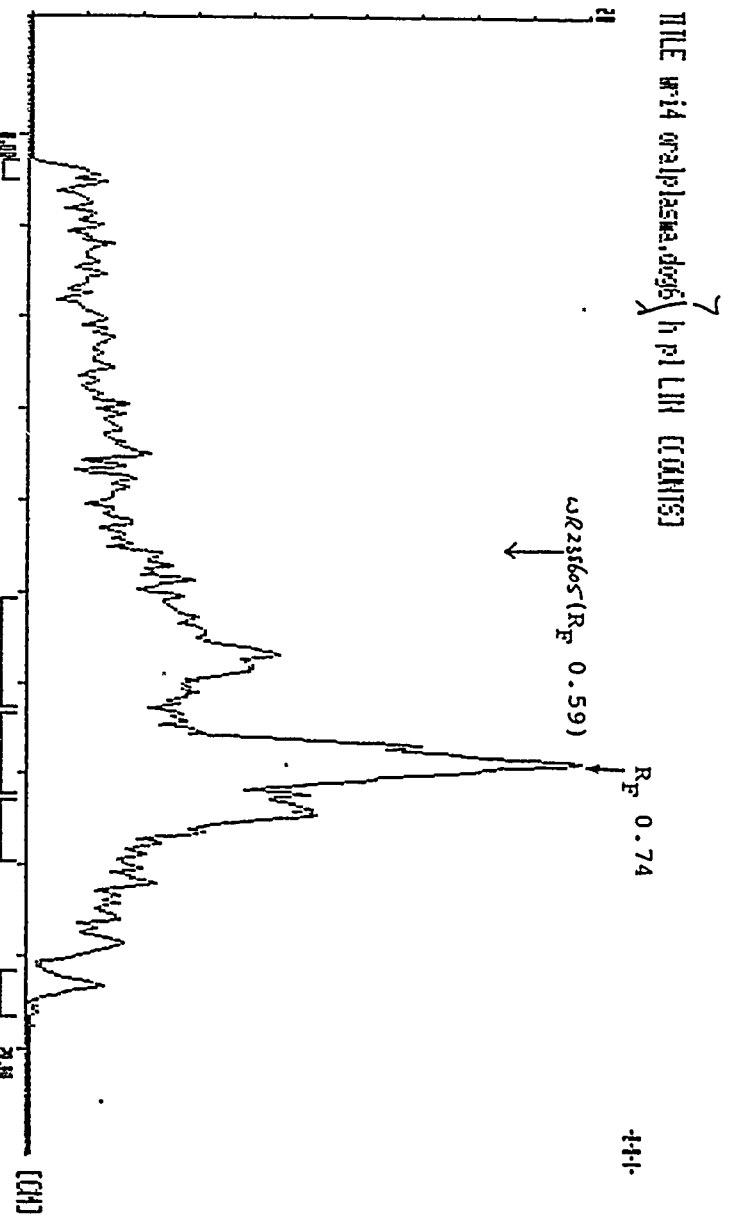


TITLE WRI 4.DOG624-48, FILE NAME 905

NUM	NAME	LEFT CHANNEL CM	RIGHT CHANNEL CM	INTEGRAL	%	NET INTEGRAL	NET %
1	BK1	0.32	0.51	86.[illegible]	[illegible]	[illegible]	[illegible]
2	2	5.86	11.24	13240.0	47.55	11574.5	45.[illegible]
3	3	11.27	15.10	14607.0	52.45	13537.5	54.[illegible]
4	BK2	19.75	19.57	55.0	[illegible]	[illegible]	[illegible]
SUM				27847.[illegible]		25.[illegible]	

FIGURE 14

Thin-layer radiochromatogram of a methanol extract of dog plasma (7 hr sample) following oral administration of ^{14}C-WR 238605 succinate (5 mg/kg). Developing solvent was methanol : 35% aqueous ammonia (25 : 1 v/v)

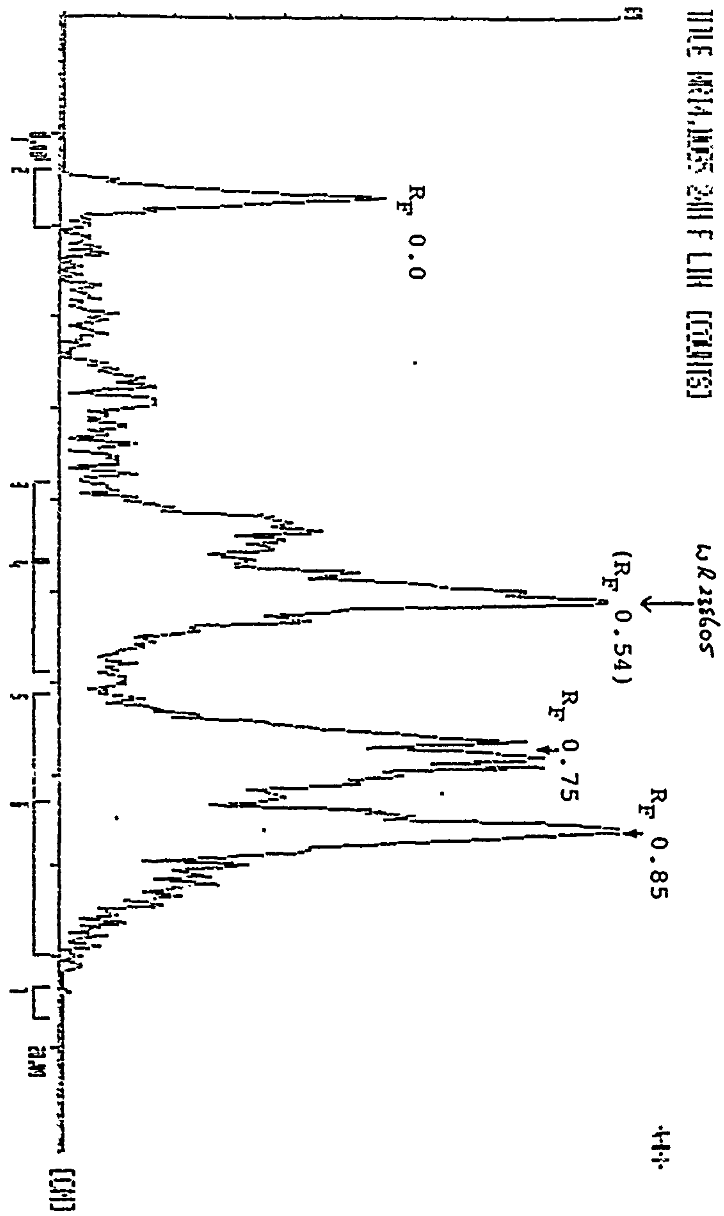


TITLE wr14 oralplasma.dog6 4h pl, FILE NAME 1001

NUM	NAME	LEFT CHANNEL CM	RIGHT CHANNEL CM	INTEGRAL	%	NET INTEGRAL	NET %
1	BK1	0.56	1.00	348.0	1.82	0.0	0.00
3		10.12	12.55	6677.0	34.85	5329.8	32.83
4		12.65	14.45	8733.0	45.57	7810.9	48.11
4		14.55	15.91	3752.0	19.58	3096.3	19.07
5	BK2	18.30	19.27	403.0	2.10	0.0	0.00
SUM				19162.0		16237.0	

FIGURE 15

Thin-layer radiochromatogram of a methanol extract of dog faeces (0-24 hr sample) following oral administration of ^{14}C-WR 238605 succinate (5 mg/kg). Developing solvent was methanol : 35% aqueous ammonia (25 : 1 v/v)



TITLE WRI4.DOGS 24H F, FILE NAME 9.8

NUM	NAME	LEFT CHANNEL CM	RIGHT CHANNEL CM	INTEGRAL	%	NET INTEGRAL	NET %
1	BK1	0.07	0.56	0.0	0.00	[illegible]	[illegible]
2	1	[illegible].73	2.00	561.0	5.95	[illegible].3	[illegible]
3	2	7.59	9.29	1158.[illegible]	12.28	115[illegible]	12.[illegible]
4	3	9.32	11.75	[illegible]	[illegible]	[illegible]7.4	[illegible]
5	4	12.24	[illegible].10	[illegible]	[illegible]	[illegible]9.3	[illegible]
6	5	14.5[illegible]	[illegible].31	[illegible]	23.74	[illegible]	23.7[illegible]
7	BK2	15.34	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SUM				[illegible]23.[illegible]		[illegible]	

THE METABOLISM AND PHARMACOKINETICS OF ^{14}C-WR 238605 IN BEAGLE DOGS AND IN THE RHESUS MONKEY

SUMMARY

1. The purpose of this study was to investigate the absorption, excretion and metabolism of the antimalarial drug WR 238605 in the beagle dog and the influence of dose levels on these parameters. In addition some comparative studies have been performed in the rhesus monkey. Studies have been carried out using ^{14}C-WR 238605 succinate after oral doses of 1.7, 3.9, 8.7 and 19.5 mg free base/kg bodyweight to beagle dogs, 0.936 mg free base/kg to rhesus monkeys and an intravenous dose of 0.936 mg free base/kg to beagle dogs.

2. After a single intravenous dose of 0.936 mg WR 238605 free base/kg to beagle dogs excretion of radioactivity was very slow and only about 60% of the dose was recovered in the excreta after 10 days. During this time means of 18.1% and 41.2% dose were excreted in urine and faeces respectively. Means of 0.9% and 1.5% dose were still excreted in urine and faeces respectively during the tenth day.

Following the intravenous administration of the same doses to the three male beagle dogs, the mean concentration of WR 238605 in plasma declined from 0.275 µg/ml 5 minutes after injection in an apparently multi-exponential pattern to 0.005 µg/ml 168 hours after dosing and was below the limit of detection of the HPLC assay in all three animals by 336 hours after dosing. The mean concentrations of total radioactivity in the same plasma samples declined from 0.377 µg equivalents WR 238605 free base 5 minutes after dosing to about 0.1 µg equivalent/ml 3-5 hours after dosing then increased again to a maximum of 0.162 µg equivalents/ml 72 hours after dosing and declined to 0.010 µg equivalents/ml 840 hours after dosing. The mean terminal half-lives for the decline in plasma concentration of WR 238605 and total radioactivity were 63.1 and 182 hours respectively. The areas under the WR 238605 concentration and total radioactivity concentration time curves were 3.9 and 56 µg.hr.ml^{-1} respectively.

The mean concentration of total radioactivity in whole-blood declined initially from 0.410 µg equivalents/ml 5 minutes after dosing to 0.108 µg equivalents/ml at 3 hours after dosing over which time concentrations of radioactivity in whole-blood were marginally greater than those in the corresponding plasma samples. After 3 hours the mean concentrations of radioactivity in whole-blood increased to a maximum of 0.220-0.235 µg equivalents during the period 48-144 hours after dosing and then declined. During this time radioactivity concentrations in blood were about 1.5-fold those in plasma samples.

Chromatography of urine and extracts of pooled 72-168 hour plasmas indicated the presence of essentially one metabolite with no WR 238605 being detected in urine samples. The metabolite is known from a previous study to be precipitated from plasma by addition of methanol and is therefore almost totally and probably irreversibly bound to plasma protein. Thin-layer chromatography indicated the metabolite to be less polar than WR 238605, but in contrast it extracted only very poorly into organic solvents such as ethyl acetate. It was unaffected by prolonged incubation with β-glucuronidase, aryl-sulphatase or protease or by an attempted acid hydrolysis and when isolated a mass spectrum could not be obtained by either Electron Impact (EI) or Chemical Ionisation (CI) procedures which were successful with WR 238605 itself.

3. When ^{14}C-WR 238605 was administered orally to groups of three dogs as a suspension in an aqueous solution of carboxymethylcellulose at dose levels of 1.7 or 3.9 mg WR 238605 free base/kg no adverse effects were observed. Upon the administration in similar fashion of doses of 8.7 or 19.5 mg WR 238605 free base/kg each of the six dogs vomited at least part (up to about 15%) of the dose within 2 hours of dosing but subsequently showed no further adverse effects.

After the low level oral dose of 1.7 mg/kg the pattern of excretion of radioactivity was very similar to that after an intravenous dose. During 10 days means of 15.9% and 40.5% dose were excreted in urine and faeces respectively. Means of 0.8% dose and 1.7% dose were excreted in urine and faeces respectively during the tenth day and the total recovery was a mean of 57.7% dose.

The patterns of excretion of radioactivity were also similar throughout the oral dose range 3.7 to 19.5 mg/kg with total mean recoveries of 55 to 56% dose during 10 days. At 3.9, 8.7 and 19.5 mg/kg the mean urine excretions of radioactivity were 10.4, 10.7 and 5.3% dose respectively in the 10 days following administration. These low overall recoveries were considered to reflect prolonged retention of radioactivity within the animal body, since at each dose level significant amounts of radioactivity were still being excreted on Day 10 of the studies. At the 8.7 and 19.5 mg/kg dose levels additional collections of excreta were made during the 24 hours of Day 35 after dosing. Even at this time means of 0.09 and 0.17% of the 8.7 mg/kg doses and 0.09 and 0.16% respectively of the 19.5 mg/kg doses were excreted in urine and faeces respectively.

Following the oral administration of ^{14}C-WR 238605 succinate to dogs as a suspension in aqueous carboxymethylcellulose at each of the four dose levels maximum concentrations of WR 238605 were measured in plasma between 3 and 12 hours after dosing. Maximum mean concentrations were 0.091, 0.241 µg WR 238605 free base/ml at 1.7 and 3.9 mg WR 238605 free base/kg and were 0.450 and 0.665 µg WR 238605 free base/ml following administration of 8.7 and 19.5 mg/kg respectively. The terminal half-lives for WR 238605 showed large interanimal variation with mean values of 54.2, 165.2, 75.0 and 138.1 hours for the doses of 1.7, 3.9, 8.7 and 19.5 mg/kg respectively. Variation in half-life was also reflected in the areas under the WR 238605 concentration versus time curves which gave mean values of 5.1, 31.8, 38.7 and 115.8 µg.hr.ml^{-1} respectively and could not be correlated with dose level.

Maximum concentrations of total radioactivity in the same plasma samples for all four dose levels were greater and occurred much later than the maximum plasma concentrations of WR 238605 at the corresponding dose levels. With increasing dose level the plasma-radioactivity profile showed a plateau rather than a peak and, at the 8.7 and 19.5 mg/kg dose levels, was subject to considerable inter-animal variation. Mean maximum plasma concentrations of radioactivity of 0.264 and 0.422 µg equivalents/ml plasma were seen 72 hours after the administration of 1.7 and 3.9 mg/kg doses respectively. Maximum concentrations of radioactivity in plasma following the 8.7 mg/kg dose ranged between 1.14 and 1.20 µg equivalents/ml during 72-144 hours after dosing and following the 19.5 mg/kg dose ranged between 0.53 and 1.63 µg equivalents/ml during 96-168 hours after dosing. Mean concentrations of WR 238605 accounted for 54-87% of total radioactivity in the 0.5 hour plasma samples but the proportion declined at each dose level, accounting for 10-30% of mean total radioactivity in plasma samples where radioactivity concentration was maximal.

The mean terminal half-lives for total radioactivity in plasma for the four dose levels were consistent, being about 200 hours. Because of the low proportion of WR 238605 in plasma during this phase of the study this half-life is effectively that of the major metabolite of ^{14}C-WR 238605.

Mean concentrations of radioactivity in whole-blood were maximal following the administration of 1.7 mg/kg WR 238605 at 0.399-0.452 µg equivalents/ml during 30-96 hours after dosing, at the 3.9 mg/kg dose level about 0.87 equivalents/ml during 96-168 hours, at the 8.7 mg/kg dose level a mean maximum of 5.55 µg equivalents/ml 120 hours after dosing and at the 19.5 mg/kg dose level 1.18-9.92 µg/equivalents/ml 120-240 hours after dosing. It was notable that, in the period shortly after dosing (where WR 238605 accounted for a large proportion of radioactivity), concentrations of radioactivity in whole-blood only marginally exceeded those in the corresponding plasma samples, whereas, at peak blood radioactivity concentrations, concentrations of radioactivity in blood cells were up to five-fold those in plasma, indicating considerable uptake of the metabolite but not WR 238605 into red blood cells.

Thin-layer chromatography of extracts of urine and plasma indicated a pattern of metabolism similar to that seen following intravenous administration of ^{14}C-WR 238605, this pattern being unaffected by the size of the oral doses administered.

4. Following a 0.94 mg/kg oral dose to rhesus monkeys excretion of radioactivity was slow, but the total mean recovery during 10 days (79.5%) was higher than in beagle dogs. During 10 days means of 56% and 20.7% dose were excreted in faeces and urine respectively. The prolonged excretion of radioactivity in faeces indicated that most of this probably represented absorbed material and that, consequently, the oral dose was well absorbed, but more rapidly excreted than in dogs.

Following the oral administration of ^{14}C-WR 238605 succinate at this dose level to the same two male rhesus monkeys maximum plasma concentrations of WR 238605 of 0.045 (24 hours) and 0.043 µg/ml (48 hours) were measured. The concentrations declined with a mean terminal half-life of 54.7 hours and the mean area under the WR 238605 concentration versus time curve was 3.34 µg.hr.ml^{-1}. Concentrations of total radioactivity in plasma were maximal at about 0.145 µg equivalents/ml plasma during 24-48 hours after dosing. The mean terminal half-life was 165.5 hours and the mean area under the plasma radioactivity concentration-time curve was 32.1 µg.hr.ml^{-1}. Concentrations of radioactivity in whole-blood were for both monkeys generally slightly (about 10%) greater than those in the corresponding plasma samples indicating that little specific uptake of radioactivity into blood cells was occurring in this species.

Thin-layer chromatography of urine extracts indicated that the metabolite formed in the dog following i.v. or oral administration of ^{14}C WR 238605 was also the major metabolite in the monkey.

5. In conclusion, in the dog the overall similarity between the excretion, metabolism and pharmacokinetics of ^{14}C-WR 238605 when administered as an intravenous dose of 0.94 free base/kg and as an oral dose of 1.7 mg free base/kg was sufficient to indicate that the latter dose was very well, if not completely absorbed from the gastro-intestinal tract. The extensive and prolonged excretion of the intravenous dose in faeces was indicative of extensive secretion of WR 238605 or its major metabolite into the intestine, probably by biliary excretion, and also possibly, in view of the prolonged excretion, of enterohepatic circulation. At the higher oral dose levels (3.9, 8.7 and 19.5 mg free base/kg) the prolonged faecal excretion of radioactivity plasma levels of WR 238605 and of radioactivity also showed that ^{14}C-WR 238605 was well absorbed from the gastro-intestinal tract.

Following the administration of each dose (i.v. or oral), concentrations of WR 238605 in plasma were generally maximal within 12 hours of dosing and subsequently declined, whereas maximum concentrations of total radioactivity were measured much later (48 hours or later, depending upon dose level). At those times where maximum radioactivity concentrations were measured, the proportions of radioactivity accounted for by WR 238605 was small, the majority of radioactivity which was extractable being associated with a single metabolite. The formation of this metabolite was paralleled by both a large uptake of radioactivity into erythrocytes and extensive and apparently irreversible binding to plasma protein and the concentrations of radioactivity in blood and plasma declined subsequently only slowly.

Although the areas under the plasma total radioactivity concentration versus time curves for the doses of 1.7, 3.9 and 8.7 mg/kg were roughly proportional, yielding values of about 50 $\mu g.hr.ml^{-1}$ when normalised for animal bodyweight and dose, at 19.5 mg/kg a mean normalised value of 30 $\mu g.hr.ml^{-1}$ was calculated. This may indicate reduced absorption of the dose or reduced reabsorption of a biliary excreted metabolite at this dose level. Both areas under the WR 238605 concentration in plasma versus time curves and their associated terminal half-lives however showed, at each dose level, considerable interanimal variation and could not be correlated with dose level. Because of the apparent interanimal variation and the complication of the analysis of the 8.7 and 19.5 mg/kg doses resulting from the partial vomiting of the dose, no in depth pharmacokinetic analysis and compartmental modelling was attempted.

Following the administration of ^{14}C-WR 238605 to two rhesus monkeys as oral doses of 0.94 mg/kg bodyweight the radioactivity was also apparently well absorbed. Comparison of the results obtained with those from the administration of the nearest dose level (1.7 mg/kg) in the dog showed that in the monkey, in the 10 days following dosing a greater proportion of the dose was excreted in both urine and faeces, giving a greater overall recovery. The general form of plasma radioactivity and WR 238605 concentration versus time curves for the two species was similar, but it was notable that the large uptake of radioactivity into erythrocytes which occurred in the dog was not seen in the monkey.

TABLE 1

Concentrations of radioactivity in the plasma of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean ± SD
	4	5	6	
0.5	0.019	0.015	0.035	0.023 ± 0.011
1	0.035	0.030	0.061	0.042 ± 0.017
2	0.055	0.050	0.072	0.059 ± 0.012
3	0.073	0.067	0.082	0.074 ± 0.008
4	0.092	0.098	0.119	0.103 ± 0.014
5	0.126	0.117	0.153	0.132 ± 0.019
7	0.155	0.144	0.183	0.161 ± 0.020
12	0.204	0.167	0.226	0.199 ± 0.030
24	0.237	0.202	0.262	0.234 ± 0.030
30	0.248	0.207	0.287	0.247 ± 0.040
48	0.266	0.217	0.291	0.258 ± 0.038
72	0.275	0.217	0.300	0.264 ± 0.043
96	0.273	0.214	0.275	0.254 ± 0.035
120	0.240	0.198	0.248	0.229 ± 0.027
144	0.228	0.179	0.221	0.209 ± 0.027
168	0.207	0.158	0.203	0.189 ± 0.027
192	0.186	0.149	0.177	0.171 ± 0.019
216	0.170	0.136	0.159	0.155 ± 0.017
240	0.152	0.128	0.148	0.143 ± 0.013
336	0.109	0.085	0.092	0.095 ± 0.012
504	0.060	0.044	0.043	0.049 ± 0.010
672	0.034	0.024	0.028	0.029 ± 0.005
840	0.019	0.013	0.015	0.016 ± 0.003

SD Standard deviation

TABLE 2

Concentrations of WR 238605 in the plasma of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Results are expressed as µg WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean
	4	5	6	
0.5	0.015	0.012	0.023	0.017
1	0.034	0.016	0.037	0.029
2	0.047	0.036	0.040	0.041
3	0.053	0.045	0.040	0.046
4	0.058	0.067	0.065	0.063
5	0.084	0.076	0.076	0.079
7	0.094	0.098	0.080	0.091
12	0.098	0.077	0.077	0.084
24	0.059	0.050	0.049	0.053
30	0.060	0.052	0.045	0.052
48	0.045	0.041	0.027	0.038
72	0.033	0.029	0.020	0.027
96	0.026	0.024	0.013	0.021
120	0.019	0.019	ND	0.013
144	0.014	0.014	ND	0.009
168	0.010	0.012	ND	0.007
192	0.010	0.011	NA	-
216	ND	ND	NA	-
240	ND	NA	NA	-

ND Not detectable (less than 10 ng/ml)
NA Not analysed

TABLE 3

Concentrations of radioactivity in the plasma of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean ± SD
	1	2	3	
0.5	0.054	0.027	0.024	0.035 ± 0.017
1	0.098	0.061	0.064	0.074 ± 0.021
2	0.137	0.118	0.125	0.127 ± 0.010
3	0.181	0.116	0.161	0.153 ± 0.033
4	0.245	0.139	0.238	0.207 ± 0.059
5	0.272	0.163	0.277	0.237 ± 0.064
7	0.314	0.207	0.340	0.287 ± 0.070
12	0.350	0.327	0.389	0.355 ± 0.031
24	0.341	0.297	0.443	0.360 ± 0.075
30	0.370	0.280	0.479	0.376 ± 0.100
48	0.346	0.303	0.475	0.375 ± 0.090
72	0.393	0.334	0.540	0.422 ± 0.106
96	0.367	0.340	0.503	0.403 ± 0.087
120	0.349	0.327	0.479	0.385 ± 0.082
144	0.334	0.319	0.391	0.348 ± 0.038
168	0.282	0.286	0.377	0.315 ± 0.054
192	0.264	0.300	0.334	0.299 ± 0.035
216	0.251	0.269	0.318	0.279 ± 0.035
240	0.233	0.254	0.291	0.259 ± 0.029
336	0.193	0.205	0.200	0.199 ± 0.006
504	0.109	0.146	0.103	0.119 ± 0.023
672	0.060	0.116	0.060	0.079 ± 0.032
840	0.033	0.073	0.033	0.046 ± 0.023

SD Standard deviation

TABLE 4

Concentrations of WR 238605 in the plasma of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Results are expressed as µg WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean
	1	2	3	
0.5	0.041	0.017	ND	0.019
1	0.078	0.049	0.038	0.055
2	0.119	0.085	0.088	0.097
3	0.153	0.099	0.113	0.122
4	0.230	0.114	0.172	0.172
5	0.218	0.137	0.185	0.180
7	0.251	0.171	0.211	0.211
12	0.259	0.265	0.199	0.241
24	0.182	0.179	0.151	0.171
30	0.182	0.159	0.178	0.173
48	0.143	0.166	0.109	0.139
72	0.143	0.140	0.086	0.123
96	0.104	0.128	0.061	0.098
120	0.089	0.110	0.047	0.082
144	0.069	0.098	0.043	0.070
168	0.067	0.082	0.026	0.058
192	0.060	0.073	0.018	0.050
216	0.045	0.067	0.017	0.043
240	0.040	0.057	0.015	0.037
336	0.031	0.043	ND	0.025
504	0.015	0.035	ND	0.017
672	ND	0.022	NA	
840	ND	0.012	NA	

ND Not detectable (less than 10 ng/ml)
NA Not analysed

TABLE 5

Concentrations of radioactivity in the plasma of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean ± SD
	4	5	6	
0.5	0.214	0.131	0.263	0.203 ± 0.067
1	0.294	0.285	0.319	0.299 ± 0.018
2	0.349	0.394	0.383	0.375 ± 0.023
3	0.504	0.610	0.564	0.559 ± 0.053
4	0.607	0.746	0.724	0.692 ± 0.075
5	0.601	0.787	0.728	0.705 ± 0.095
7	0.699	0.817	0.824	0.780 ± 0.070
12	0.730	0.840	0.914	0.828 ± 0.093
24	0.806	0.938	0.992	0.912 ± 0.096
30	0.880	0.990	1.11	0.993 ± 0.115
48	0.937	0.980	1.10	1.01 ± 0.08
72	1.05	1.10	1.26	1.14 ± 0.11
96	1.08	1.13	1.38	1.20 ± 0.16
120	1.11	1.11	1.33	1.18 ± 0.13
144	1.06	1.07	1.28	1.14 ± 0.12
168	1.03	1.05	1.24	1.11 ± 0.12
192	0.973	0.973	1.14	1.03 ± 0.10
216	0.940	0.915	1.09	0.982 ± 0.095
240	0.887	0.930	1.07	0.962 ± 0.096
336	0.697	0.716	0.761	0.725 ± 0.033
504	0.380	0.374	0.377	0.377 ± 0.003
672	0.206	0.207	0.201	0.205 ± 0.003
840	0.117	0.111	0.110	0.113 ± 0.004

SD Standard deviation

TABLE 6

Concentrations of WR 238605 in the plasma of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Results are expressed as µg WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean
	4	5	6	
0.5	0.202	0.072	0.217	0.164
1	0.230	0.209	0.254	0.231
2	0.190	0.276	0.253	0.240
3	0.404	0.450	0.390	0.415
4	0.449	0.465	0.435	0.450
5	0.427	0.391	0.440	0.419
7	0.455	0.492	0.397	0.448
12	0.358	0.388	0.327	0.358
24	0.290	0.293	0.252	0.278
30	0.311	0.334	0.311	0.319
48	0.222	0.208	0.172	0.201
72	0.197	0.210	0.169	0.192
96	0.169	0.180	0.163	0.171
120	0.150	0.147	0.109	0.135
144	0.107	0.111	0.087	0.102
168	0.078	0.098	0.065	0.080
192	0.070	0.067	0.043	0.060
216	0.058	0.054	0.036	0.049
240	0.038	0.051	0.021	0.037
336	0.021	0.024	ND	0.015
504	ND	ND	ND	ND
672	ND	ND	ND	ND
840	ND	ND	ND	ND

ND Not detectable (less than 10 ng/ml)

TABLE 7

Concentrations of radioactivity in the plasma of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean ± SD
	1	2	3	
0.5	0.416	0.126	0.311	0.284 ± 0.147
1	0.572	0.239	0.497	0.436 ± 0.175
2	0.693	0.294	0.644	0.544 ± 0.218
3	0.914	0.373	0.943	0.743 ± 0.321
4	0.951	0.406	1.03	0.796 ± 0.340
5	0.876	0.420	1.06	0.785 ± 0.329
7	0.887	0.433	1.13	0.817 ± 0.354
12	0.904	0.473	1.21	0.862 ± 0.370
24	1.03	0.470	1.29	0.930 ± 0.419
30	1.09	0.488	1.37	0.983 ± 0.451
48	1.16	0.461	1.40	1.01 ± 0.49
72	1.29	0.512	1.56	1.12 ± 0.54
96	1.32	0.545	1.63	1.17 ± 0.56
120	1.37	0.533	1.61	1.17 ± 0.57
144	1.31	0.530	1.57	1.14 ± 0.54
168	1.35	0.537	1.57	1.15 ± 0.54
192	1.23	0.514	1.50	1.08 ± 0.51
216	1.21	0.486	1.42	1.04 ± 0.49
240	1.21	0.482	1.38	1.02 ± 0.48
336	1.06	0.388	1.20	0.883 ± 0.434
504	0.634	0.260	0.707	0.534 ± 0.240
672	0.374	0.168	0.392	0.311 ± 0.124
840	0.201	0.104	0.195	0.167 ± 0.054

SD Standard deviation

TABLE 8

Concentrations of WR 238605 in the plasma of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Results are expressed as µg WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean
	1	2	3	
0.5	0.415	0.069	0.264	0.249
1	0.550	0.192	0.433	0.392
2	0.673	0.232	0.498	0.468
3	0.808	0.332	0.754	0.631
4	0.861	0.354	0.780	0.665
5	0.833	0.373	0.735	0.647
7	0.719	0.383	0.749	0.617
12	0.653	0.406	0.665	0.575
24	0.568	0.301	0.547	0.472
30	0.645	0.336	0.609	0.530
48	0.479	0.248	0.472	0.400
72	0.472	0.232	0.469	0.391
96	0.422	0.223	0.404	0.350
120	0.385	0.202	0.302	0.296
144	0.326	0.201	0.282	0.270
168	0.343	0.196	0.251	0.263
192	0.266	0.177	0.196	0.213
216	0.254	0.132	0.160	0.182
240	0.220	0.128	0.133	0.160
336	0.198	0.101	0.098	0.132
504	0.075	0.058	0.024	0.052
672	0.034	0.027	ND	0.020
840	0.014	0.014	ND	0.009

ND Not detectable (less than 10 ng/ml)

TABLE 9

Concentrations of radioactivity in the plasma of beagle dogs following administration of a single intravenous dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean ± SD
	3	4	6	
0.08	0.375	0.394	0.362	0.377 ± 0.016
0.25	0.194	0.175	0.169	0.179 ± 0.013
0.5	0.146	0.130	0.133	0.136 ± 0.009
0.75	0.153	0.110	0.129	0.131 ± 0.022
1	0.107	0.108	0.112	0.109 ± 0.003
2	0.104	0.112	0.101	0.106 ± 0.006
3	0.111	0.092	0.091	0.098 ± 0.011
4	0.101	0.110	0.105	0.105 ± 0.005
5	0.098	0.093	0.105	0.099 ± 0.006
7	0.114	0.103	0.111	0.109 ± 0.006
12	0.127	0.112	0.124	0.121 ± 0.008
24	0.134	0.119	0.147	0.133 ± 0.014
30	0.143	0.135	0.168	0.149 ± 0.017
48	0.146	0.159	0.176	0.160 ± 0.015
72	0.162	0.142	0.181	0.162 ± 0.020
96	0.143	0.134	0.175	0.151 ± 0.022
120	0.134	0.148	0.168	0.150 ± 0.017
144	0.139	0.134	0.152	0.142 ± 0.009
168	0.119	0.141	0.126	0.129 ± 0.011
192	0.101	0.097	0.119	0.106 ± 0.012
216	0.095	0.109	0.106	0.103 ± 0.007
240	0.093	0.098	0.104	0.098 ± 0.006
336	0.065	0.074	0.077	0.072 ± 0.006
504	0.032	0.037	0.034	0.034 ± 0.003
672	0.012	0.022	0.018	0.017 ± 0.005
840	0.007	0.013	0.011	0.010 ± 0.003

SD Standard deviation

TABLE 10

Concentrations of WR 238605 in the plasma of beagle dogs following administration of a single intravenous dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as µg WR 238605 free base/ml plasma

Time (hrs)	Dog number			Mean
	3	4	6	
0.08	0.278	0.262	0.284	0.275
0.25	0.117	0.101	0.106	0.108
0.5	0.085	0.065	0.074	0.075
0.75	0.074	0.062	0.073	0.070
1	0.073	0.057	0.065	0.065
2	0.064	0.057	0.059	0.060
3	0.053	0.048	0.047	0.049
4	0.056	0.041	0.051	0.049
5	0.055	0.043	0.051	0.050
7	0.058	0.047	*	0.053
12	0.050	0.042	0.043	0.045
24	0.040	0.029	0.029	0.033
30	0.039	0.030	0.034	0.034
48	0.028	0.022	0.020	0.023
72	0.020	0.014	0.013	0.016
96	0.016	0.013	0.011	0.013
120	0.013	0.009	0.009	0.010
144	0.010	0.008	0.005	0.008
168	0.008	0.005	0.003	0.005
192	0.006	0.005	ND	0.004
216	0.004	0.004	ND	0.003
240	0.004	0.004	ND	0.003
336	ND	ND	ND	ND
504	ND	ND	ND	ND

ND Not detectable (less than 2.5 ng/ml)
* Insufficient sample for analysis

TABLE 11

Concentrations of radioactivity in the plasma of rhesus monkeys following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml plasma

Time (hrs)	Monkey number		Mean
	H179	J625	
0.5	ND	0.004	0.002
1	0.005	0.011	0.008
2	0.028	0.025	0.027
3	0.046	0.042	0.044
4	0.066	0.049	0.058
5	0.077	0.049	0.063
7	0.101	0.075	0.088
12	0.136	0.106	0.121
24	0.139	0.127	0.133
30	0.140	0.134	0.137
48	0.122	0.149	0.136
72	0.115	0.127	0.121
120	0.092	0.093	0.093
144	0.078	0.079	0.079
168	0.072	0.071	0.072
192	0.063	0.061	0.062
216	0.054	0.055	0.055
240	0.046	0.048	0.047
264	0.038	0.043	0.041
288	0.037	0.038	0.038
312	0.032	0.034	0.033
336	0.029	0.030	0.030
504	0.014	0.014	0.014
672	0.008	0.008	0.008
840	0.005	0.005	0.005

ND Not detectable

TABLE 12

Concentrations of WR 238605 in the plasma of rhesus monkeys following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as ng WR 238605 free base/ml plasma

Time (hrs)	Monkey number		Mean
	J625	H179	
0.5	ND	ND	-
1	2.6	ND	-
2	5.3	7.4	6.4
3	6.6	13.3	10.0
4	10.5	16.4	13.5
5	10.0	12.0	11.0
7	18.8	25.0	21.9
12	21.8	33.2	27.5
24	44.5	28.1	36.3
30	41.1	26.6	33.8
48	25.6	43.3	34.5
72	16.0	23.7	19.9
120	NA	12.6	12.6
144	7.6	5.1	6.4
168	4.9	NA	4.9
192	NA	NA	-
216	3.5	2.8	3.2
240	ND	ND	-
264	ND	ND	-
288	ND	NS	-

ND Not detectable (<2.5 ng/ml plasma)
NS No sample
NA No analysis of these samples possible due to interference by another peak with WR 238605 peak

TABLE 13

Concentrations of radioactivity in the whole-blood of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml blood

Time (hrs)	Dog number			Mean ± SD
	4	5	6	
0.5	ND	ND	0.021	0.007 ± 0.012
1	0.031	0.020	0.043	0.031 ± 0.012
2	0.057	0.049	0.059	0.055 ± 0.005
3	0.076	0.072	0.079	0.076 ± 0.004
4	0.105	0.116	0.127	0.116 ± 0.011
5	0.150	0.141	0.165	0.152 ± 0.012
7	0.193	0.172	0.191	0.185 ± 0.012
12	0.276	0.197	0.273	0.249 ± 0.045
24	0.313	0.317	0.336	0.322 ± 0.012
30	0.435	0.373	0.390	0.399 ± 0.032
48	0.410	0.376	0.402	0.396 ± 0.018
72	0.461	0.384	0.437	0.427 ± 0.039
96	0.499	0.463	0.394	0.452 ± 0.053
120	0.419	0.342	0.362	0.374 ± 0.040
144	0.437	0.381	0.347	0.388 ± 0.045
168	0.456	0.334	0.333	0.374 ± 0.071
192	0.390	0.312	0.293	0.332 ± 0.051
216	0.355	0.296	0.255	0.302 ± 0.050
240	0.308	0.300	0.228	0.279 ± 0.044
336	0.233	0.185	0.171	0.196 ± 0.033
504	0.165	0.115	0.112	0.131 ± 0.030
672	0.103	0.079	0.070	0.084 ± 0.017
840	0.075	0.066	0.093	0.078 ± 0.014

SD Standard deviation
ND Not detectable

TABLE 14

Concentrations of radioactivity in the whole-blood of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml blood

Time (hrs)	Dog number			Mean ± SD
	1	2	3	
0.5	0.035	ND	ND	0.012 ± 0.020
1	0.076	0.046	0.043	0.055 ± 0.018
2	0.136	0.101	0.103	0.113 ± 0.020
3	0.180	0.121	0.151	0.151 ± 0.030
4	0.243	0.142	0.233	0.206 ± 0.056
5	0.274	0.177	0.322	0.258 ± 0.074
7	0.347	0.257	0.394	0.333 ± 0.070
12	0.364	0.347	0.556	0.422 ± 0.116
24	0.401	0.331	0.768	0.500 ± 0.235
30	0.452	0.290	0.998	0.580 ± 0.371
48	0.463	0.404	1.09	0.652 ± 0.380
72	0.573	0.476	1.25	0.766 ± 0.422
96	0.556	0.504	1.39	0.817 ± 0.497
120	0.570	0.485	1.53	0.862 ± 0.580
144	0.594	0.488	1.56	0.881 ± 0.591
168	0.589	0.456	1.56	0.868 ± 0.603
192	0.559	0.486	1.20	0.748 ± 0.393
216	0.532	0.468	1.22	0.740 ± 0.417
240	0.480	0.411	1.18	0.690 ± 0.425
336	0.387	0.374	0.864	0.542 ± 0.279
504	0.258	0.267	0.457	0.327 ± 0.112
672	0.179	0.210	0.286	0.225 ± 0.055
840	0.135	0.153	0.154	0.147 ± 0.011

SD Standard deviation
ND Not detectable

TABLE 15

Concentrations of radioactivity in the whole-blood of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml blood

Time (hrs)	Dog number			Mean ± SD
	4	5	6	
0.5	0.240	0.108	0.248	0.199 ± 0.079
1	0.321	0.287	0.351	0.320 ± 0.032
2	0.418	0.417	0.435	0.423 ± 0.010
3	0.600	0.674	0.657	0.644 ± 0.039
4	0.810	0.986	0.940	0.912 ± 0.091
5	0.883	1.07	1.03	0.994 ± 0.098
7	1.10	1.32	1.30	1.24 ± 0.12
12	1.42	1.73	1.85	1.67 ± 0.22
24	1.81	2.36	2.30	2.16 ± 0.30
30	2.19	2.97	3.00	2.72 ± 0.46
48	2.88	3.37	3.10	3.12 ± 0.25
72	3.70	4.49	4.62	4.27 ± 0.50
96	4.65	4.83	5.32	4.93 ± 0.35
120	5.10	5.61	5.94	5.55 ± 0.42
144	4.63	5.48	5.79	5.30 ± 0.60
168	4.64	5.41	5.41	5.15 ± 0.44
192	4.20	4.75	5.29	4.75 ± 0.55
216	4.26	5.06	5.20	4.84 ± 0.51
240	3.86	4.50	5.21	4.52 ± 0.68
336	2.91	3.65	3.63	3.40 ± 0.42
504	1.28	1.55	1.89	1.57 ± 0.31
672	0.569	0.833	1.16	0.854 ± 0.296
840	0.275	0.421	0.623	0.440 ± 0.175

SD Standard deviation

TABLE 16

Concentrations of radioactivity in the whole-blood of beagle dogs following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml blood

Time (hrs)	Dog number			Mean ± SD
	1	2	3	
0.5	0.426	ND	0.286	0.237 ± 0.217
1	0.473	0.253	0.488	0.405 ± 0.132
2	0.799	0.296	0.685	0.593 ± 0.264
3	1.01	0.408	1.06	0.826 ± 0.363
4	1.15	0.492	1.39	1.01 ± 0.46
5	1.18	0.502	1.41	1.03 ± 0.47
7	1.27	0.566	1.67	1.17 ± 0.56
12	1.52	0.673	2.35	1.51 ± 0.84
24	1.91	0.711	3.04	1.89 ± 1.16
30	2.38	0.753	3.72	2.28 ± 1.49
48	2.80	0.772	4.44	2.67 ± 1.84
72	3.67	0.860	5.59	3.37 ± 2.38
96	4.39	1.03	6.80	4.07 ± 2.90
120	4.60	1.21	9.92	5.24 ± 4.39
144	4.95	1.14	7.43	4.51 ± 3.17
168	5.39	1.22	7.78	4.80 ± 3.32
192	4.98	1.19	7.74	4.64 ± 3.29
216	5.08	1.18	8.10	4.79 ± 3.47
240	5.22	1.21	8.06	4.83 ± 3.44
336	4.96	0.993	7.24	4.40 ± 3.16
504	2.87	0.642	3.87	2.46 ± 1.65
672	1.55	0.458	1.67	1.23 ± 0.67
840	0.801	0.319	0.681	0.600 ± 0.251

SD Standard deviation
ND Not detectable

TABLE 17

Concentrations of radioactivity in the whole-blood of beagle dogs follcwing administration of a single intravenous dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml blood

Time (hrs)	Dog number			Mean ± SD
	3	4	6	
0.08	0.397	0.420	0.414	0.410 ± 0.012
0.25	0.205	0.199	0.198	0.201 ± 0.004
0.5	0.153	0.150	0.154	0.152 ± 0.002
0.75	0.134	0.132	0.143	0.136 ± 0.006
1	0.123	0.121	0.127	0.124 ± 0.003
2	0.112	0.115	0.115	0.114 ± 0.002
3	0.108	0.110	0.106	0.108 ± 0.002
4	0.110	0.108	0.122	0.113 ± 0.008
5	0.115	0.114	0.127	0.119 ± 0.007
7	0.125	0.120	0.130	0.125 ± 0.005
12	0.148	0.137	0.159	0.148 ± 0.011
24	0.161	0.166	0.184	0.170 ± 0.012
30	0.183	0.180	0.221	0.195 ± 0.023
48	0.207	0.217	0.237	0.220 ± 0.015
72	0.224	0.234	0.247	0.235 ± 0.012
96	0.227	0.207	0.254	0.229 ± 0.024
120	0.221	0.231	0.213	0.222 ± 0.009
144	0.213	0.220	0.233	0.222 ± 0.010
168	0.193	0.203	0.170	0.189 ± 0.017
192	0.186	0.193	0.198	0.192 ± 0.006
216	0.162	0.180	0.149	0.164 ± 0.016
240	0.156	0.152	0.171	0.160 ± 0.010
336	0.120	0.119	0.115	0.118 ± 0.003
504	0.065	0.067	0.067	0.066 ± 0.001
672	0.040	0.046	0.046	0.044 ± 0.003
840	0.027	0.035	0.032	0.031 ± 0.004

SD Standard deviation

TABLE 18

Concentrations of radioactivity in the whole-blood of rhesus monkeys following administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as µg equivalents of WR 238605 free base/ml blood

Time (hrs)	Monkey number		Mean
	H179	J625	
0.5	ND	ND	-
1	ND	0.0150	0.0075
2	0.0348	0.0309	0.0329
3	0.0512	0.0529	0.0521
4	0.0763	0.0617	0.0690
5	0.0815	0.0612	0.0714
7	0.101	0.101	0.101
12	0.142	0.124	0.133
24	0.152	0.144	0.148
30	0.151	0.147	0.149
48	0.134	0.154	0.144
72	0.128	0.141	0.135
96	0.117	0.127	0.122
120	0.102	0.111	0.107
144	0.0862	0.0996	0.0929
168	0.0756	0.0847	0.0802
192	0.0668	0.0747	0.0708
216	0.0561	0.0682	0.0622
240	0.0462	0.0588	0.0525
264	0.0410	0.0527	0.0469
288	0.0411	0.0501	0.0456
312	0.0359	0.0447	0.0403
336	0.0291	0.0424	0.0358
504	0.0183	0.0239	0.0211
672	ND	0.0119	0.0060
840	ND	ND	-

ND Not detectable

TABLE 19

Pharmacokinetic parameters calculated from the concentrations of radioactivity in the plasma of beagle dogs following oral administration of ^{14}C-WR 238605 succinate

Dose level (mg WR 238605 free base/kg)	1.7				3.9			
Dog number	4	5	6	Mean	1	2	3	Mean
Maximum concentration (µg equivalents/ml)	0.275	0.217	0.3000	-	0.390	0.340	0.540	-
Terminal half-life (hours) ($T_{\frac{1}{2}}$)	195.2	186.6	174.4	185.4	213.4	339.4	184.6	245.8
Time over which $T_{\frac{1}{2}}$ calculated (hours after dosing)	72-840	48-840	72-840	-	72-840	96-840	72-840	-
AUC (area under plasma concentration/time curve; $\mu g.hr.ml^{-1}$)	92.21	72.64	87.24	84.03	143.50	162.90	168.90	158.4
AUC normalised for dose and bodyweight ($\mu g.hr.ml^{-1}/mg/kg$) [a]	58.0	45.4	57.4	53.6	39.5	43.8	46.1	43.1
Bioavailability [b] (% dose)	101	79	100	93	69	76	80	75

a $\frac{\text{AUC}}{\text{actual dose administered in mg/kg bodyweight}}$ (Appendix 1, Table 2)

b $\frac{\text{AUC (normalised) oral dose}}{\text{AUC (normalised) intravenous dose}}$

TABLE 19

(continued)

Dose level (mg WR 238605 free base/kg)	8.7				19.5			
Dog number	4	5	6	Mean	1	2	3	Mean
Maximum concentration (µg equivalents/ml)	1.11	1.13	1.38	-	1.37	0.545	1.63	-
Terminal half-life (hours) ($T_{\frac{1}{2}}$)	210.8	206.2	188.5	201.8	227.8	271.9	223.9	241.2
Time over which $T_{\frac{1}{2}}$ calculated (hours after dosing)	168-840	168-840	168-840	-	240-840	240-840	192-840	-
AUC (area under plasma concentration/time curve; $\mu g.hr.ml^{-1}$)	476.20	487.70	539.40	501.10	678.70	275.80	779.30	577.93
AUC normalised for dose and bodyweight ($\mu g.hr.ml^{-1}/mg/kg$) [a]	53.1	54.2	60.1	55.8	35.2	14.2	39.3	29.6
Bioavailability [b] (% dose)	92	94	104	97	61	25	68	51

a $\frac{\text{AUC}}{\text{actual dose administered in mg/kg bodyweight}}$ (Appendix 1, Table 2)

b $\frac{\text{AUC (normalised) oral dose}}{\text{AUC (normalised) intravenous dose}}$

TABLE 20

Pharmacokinetic parameters calculated from the concentration of WR 238605 in the plasma of beagle dogs following oral administration of ^{14}C-WR 238605 succinate

Dose level (mg WR 238605 free base/kg)	1.7				3.9			
Dog number	4	5	6	Mean	1	2	3	Mean
t max (hours)	12	7	7	-	12	12	7	-
Maximum concentration (µg equivalents/ml)	0.098	0.098	0.080	-	0.259	0.265	0.211	-
Terminal half-life (hours) ($T_{\frac{1}{2}}$)	55.9	68.0	38.6	54.2	156.0	273.9	65.7	165.2
Time over which $T_{\frac{1}{2}}$ calculated (hours after dosing)	48-168	48-168	30- 96	-	120-504	216-840	120-240	-
AUC (area under plasma concentration/time curve; µg.hr.ml^{-1})	6.243	5.697	3.417	5.119	32.413	46.837	16.225	31.825
AUC normalised for dose and bodyweight (µg.hr.ml^{-1}/mg/kg) [a]	3.926	3.561	2.248	3.245	8.929	12.591	4.433	8.651
Bioavailability [b] (% dose)	99	90	57	82	225	317	112	218

a $\frac{\text{AUC}}{\text{actual dose administered in mg/kg bodyweight}}$ (Appendix 1, Table 2)

b $\frac{\text{AUC (normalised) oral dose}}{\text{AUC (normalised) intravenous dose}}$

TABLE 20

(continued)

Dose level (mg WR 238605 free base/kg)	8.7				19.5			
Dog number	4	5	6	Mean	1	2	3	Mean
t max (hours)	7	7	5	-	4	12	4	-
Maximum concentration (µg equivalents/ml)	0.455	0.492	0.440	-	0.861	0.406	0.780	-
Terminal half-life (hours) ($T_{\frac{1}{2}}$)	85.1	88.5	51.4	75.0	133.2	174.0	107.1	138.1
Time over which $T_{\frac{1}{2}}$ calculated (hours after dosing)	168-336	168-336	96-240	-	336-840	336-840	216-504	-
AUC (area under plasma concentration/time curve; $\mu g.hr.ml^{-1}$)	40.781	43.023	32.198	38.667	153.246	87.577	106.476	115.766
AUC normalised for dose and bodyweight ($\mu g.hr.ml^{-1}/mg/kg$) [a]	4.551	4.780	3.586	4.306	7.948	4.503	5.375	5.942
Bioavailability [b] (% dose)	115	120	90	108	200	113	135	149

a $\frac{\text{AUC}}{\text{actual dose administered in mg/kg bodyweight}}$ (Appendix 1, Table 2)

b $\frac{\text{AUC (normalised) oral dose}}{\text{AUC (normalised) intravenous dose}}$

TABLE 21

Pharmacokinetic parameters calculated from the concentration of radioactivity in the whole-blood of beagle dogs following oral administration of ^{14}C-WR 238605 succinate

Dose level (mg WR 238605 free base/kg)	1.7				3.9			
Dog number	4	5	6	Mean	1	2	3	Mean
Maximum concentration (µg equivalents/ml)	0.499	0.463	0.437	-	0.590	0.500	1.56	-
Terminal half-life (hours) ($T_{\frac{1}{2}}$)	266.9	258.7	298.6	274.7	316.1	421.0	208.7	315.3
Time over which $T_{\frac{1}{2}}$ calculated (hours after dosing)	96-840	96-840	96-840	-	144-840	96-840	144-840	-
AUC (area under plasma concentration/time curve; µg.hr.ml^{-1})	193.10	158.80	152.40	168.1	285.20	267.00	604.90	385.70
AUC normalised for dose and bodyweight (µg.hr.ml^{-1}/mg/kg) [a]	121.4	99.3	100.3	-	78.6	71.8	165.3	-

a $\frac{\text{AUC}}{\text{actual dose administered in mg/kg bodyweight}}$ (Appendix 1, Table 2)

TABLE 21

(continued)

Dose level (mg WR 238605 free base/kg)	8.7				19.5			
Dog number	4	5	6	Mean	1	2	3	Mean
Maximum concentration (µg equivalents/ml)	5.10	5.61	5.94	-	5.39	1.22	9.92	-
Terminal half-life (hours) ($T_{\frac{1}{2}}$)	155.5	172.0	197.9	175.1	213.8	309.6	163.9	229.1
Time over which $T_{\frac{1}{2}}$ calculated (hours after dosing)	216-840	216-840	240-840	-	240-840	240-840	240-840	-
AUC (area under plasma concentration/time curve; $\mu g.hr.ml^{-1}$)	1820.00	2194.00	2404.00	2139.33	2698.00	644.70	3905.00	2415.90
AUC normalised for dose and bodyweight ($\mu g.hr.ml^{-1}/mg/kg$) [a]	203.1	243.8	267.7	-	139.9	33.1	197.1	-

a $\frac{\text{AUC}}{\text{actual dose administered in mg/kg bodyweight}}$ (Appendix 1, Table 2)

TABLE 22

Pharmacokinetic parameters calculated from the concentration of radioactivity and WR 238605 in the plasma of beagle dogs following intravenous administration of ^{14}C-WR 238605 succinate

	WR 238605				Total radioactivity			
Dog number	3	4	6	Mean	3	4	6	Mean
Maximum concentration (µg equivalents/ml)	0.278	0.262	0.284	-	0.375	0.394	0.362	-
Terminal half-life (hours) ($T_{\frac{1}{2}}$)	67.2	76.9	45.1	63.1	160.9	203.3	182.0	182.0
Time over which $T_{\frac{1}{2}}$ calculated (hours after dosing)	72-240	72-240	48-168	-	144-840	144-840	144-840	-
AUC (area under plasma concentration/time curve; µg.hr.ml^{-1})	4.701	3.778	3.130	3.870	51.7	56.4	59.9	56.0
AUC normalised for dose and bodyweight (µg.hr.ml^{-1}/mg/kg) [a]	4.812	3.879	3.227	3.973	52.917	57.906	61.753	57.525

a $\frac{\text{AUC}}{\text{actual dose administered in mg/kg bodyweight}}$ (Appendix 1, Table 3)

TABLE 23

Pharmacokinetic parameters calculated from the concentrations of radioactivity in the whole-blood of beagle dogs following the intravenous administration of ^{14}C-WR 238605 succinate at a nominal dose level of 0.936 WR 238605 free base/kg

Dose level (mg WR 238605 free base/kg)	0.936			
Dog number	3	4	6	Mean
Maximum concentration (µg equivalents/ml)	0.227	0.234	0.254	-
Terminal half-life (hours) ($T_{½}$)	227.9	252.6	252.0	244.2
Time over which $T_{½}$ calculated (hours after dosing)	144-840	168-840	240-840	-
AUC (area under plasma concentration/time curve; µg.hr.ml^{-1})	89.64	92.57	94.17	92.13
AUC normalised for dose and bodyweight (µg.hr.ml^{-1}/mg/kg) [a]	91.75	95.04	97.08	94.62

a $\frac{\text{AUC}}{\text{actual dose administered in mg/kg bodyweight}}$ (Appendix 1, Table 3)

TABLE 24

Pharmacokinetic parameters calculated from the concentrations of radioactivity in whole-blood and plasma and the concentration of WR 238605 in the plasma of rhesus monkeys following oral administration of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

	Concentration of radioactivity in plasma			Concentration of WR 238605 in plasma			Concentration of radioactivity in whole-blood		
Monkey number	H179	J625	Mean	H179	J625	Mean	H179	J625	Mean
Maximum concentration (µg equivalents/ml)	0.140	0.149	-	0.043	0.045	-	0.152	0.154	-
Terminal half-life (hours) ($T_{\frac{1}{2}}$)	168.9	162.1	165.5	45.5	63.9	54.7	196.0	190.9	193.4
Time over which $T_{\frac{1}{2}}$ calculated (hours after dosing)	72-840	72-840	-	72-216	72-216	-	240-504	240-672	-
AUC (area under plasma concentration/time curve; µg.hr.ml^{-1})	31.7	32.5	32.1	3.559	3.115	3.337	32.8	39.9	36.4

TABLE 25

The excretion of radioactivity by beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		4	5	6	
Faeces	0- 24	5.50	8.56	9.76	7.94 ± 2.20
	24- 48	6.93	7.51	6.83	7.09 ± 0.37
	48- 72	7.55	4.44	3.25	5.08 ± 2.22
	72- 96	3.49	4.73	5.47	4.56 ± 1.00
	96-120	5.61	2.72	3.11	3.81 ± 1.57
	120-144	3.17	4.06	2.93	3.39 ± 0.60
	144-168	2.53	2.26	2.51	2.43 ± 0.15
	168-192	2.52	2.85	1.99	2.45 ± 0.43
	192-216	2.00	2.28	1.93	2.07 ± 0.19
	216-240	1.82	1.85	1.41	1.69 ± 0.25
	Total	41.12	41.26	39.19	40.52 ± 1.16
Urine	0- 6	0.26	0.11	0.34	0.24 ± 0.12
	6- 24	2.07	2.28	2.37	2.24 ± 0.15
	24- 48	2.25	2.14	2.77	2.39 ± 0.34
	48- 72	2.18	1.93	2.14	2.08 ± 0.13
	72- 96	2.11	1.75	2.03	1.96 ± 0.19
	96-120	1.36	1.54	1.70	1.53 ± 0.17
	120-144	1.48	1.34	1.50	1.44 ± 0.09
	144-168	1.41	1.18	1.24	1.28 ± 0.12
	168-192	1.06	0.97	1.00	1.01 ± 0.05
	192-216	1.10	0.94	0.87	0.97 ± 0.12
	216-240	0.91	0.66	0.76	0.78 ± 0.13
	Total	16.19	14.84	16.72	15.92 ± 0.97
Cage wash	0- 24	0.15	0.20	0.46	0.27 ± 0.17
	24- 48	0.16	0.15	0.23	0.18 ± 0.04
	48- 72	0.20	0.12	0.27	0.20 ± 0.08
	72- 96	0.14	0.09	0.21	0.15 ± 0.06
	96-120	0.13	0.08	0.07	0.09 ± 0.03
	120-144	0.07	0.04	0.06	0.06 ± 0.02
	144-168	0.06	0.05	0.10	0.07 ± 0.03
	168-192	0.06	0.05	0.05	0.05 ± 0.01
	192-216	0.08	0.11	0.10	0.10 ± 0.02
	216-240	0.10	0.06	NS	0.05 ± 0.05
	Total	1.15	0.95	1.55	1.22 ± 0.31
	Overall total	58.46	57.05	57.46	57.66 ± 0.73

SD Standard deviation
NS No sample

TABLE 26

Cumulative excretion of radioactivity by beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		4	5	6	
Faeces	0- 24	5.50	8.56	9.76	7.94 ± 2.20
	0- 48	12.43	16.07	16.59	15.03 ± 2.27
	0- 72	19.98	20.51	19.84	20.11 ± 0.35
	0- 96	23.47	25.24	25.31	24.67 ± 1.04
	0-120	29.08	27.96	28.42	28.49 ± 0.56
	0-144	32.25	32.02	31.35	31.87 ± 0.47
	0-168	34.78	34.28	33.86	34.31 ± 0.46
	0-192	37.30	37.13	35.85	36.76 ± 0.79
	0-216	39.30	39.41	37.78	38.83 ± 0.91
	0-240	41.12	41.26	39.19	40.52 ± 1.16
Urine	0- 6	0.26	0.11	0.34	0.24 ± 0.12
	0- 24	2.33	2.39	2.71	2.48 ± 0.20
	0- 48	4.58	4.53	5.48	4.86 ± 0.53
	0- 72	6.76	6.46	7.62	6.95 ± 0.60
	0- 96	8.87	8.21	9.65	8.91 ± 0.72
	0-120	10.23	9.75	11.35	10.44 ± 0.82
	0-144	11.71	11.09	12.85	11.88 ± 0.89
	0-168	13.12	12.27	14.09	13.16 ± 0.91
	0-192	14.18	13.24	15.09	14.17 ± 0.93
	0-216	15.28	14.18	15.96	15.14 ± 0.90
	0-240	16.19	14.84	16.72	15.92 ± 0.97
Cage wash	0- 24	0.15	0.20	0.46	0.27 ± 0.17
	0- 48	0.31	0.35	0.69	0.45 ± 0.21
	0- 72	0.51	0.47	0.96	0.65 ± 0.27
	0- 96	0.65	0.56	1.17	0.79 ± 0.33
	0-120	0.78	0.64	1.24	0.89 ± 0.31
	0-144	0.85	0.68	1.30	0.94 ± 0.32
	0-168	0.91	0.73	1.40	1.01 ± 0.35
	0-192	0.97	0.78	1.45	1.07 ± 0.35
	0-216	1.05	0.89	1.55	1.16 ± 0.34
	0-240	1.15	0.95	1.55	1.22 ± 0.31
	Overall total	58.46	57.05	57.46	57.66 ± 0.73

SD Standard deviation

TABLE 27

The excretion of radioactivity by beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		1	2	3	
Faeces	0- 24	12.21	10.15	18.49	13.62 ± 4.34
	24- 48	7.54	4.51	7.09	6.38 ± 1.64
	48- 72	3.02	6.02	4.97	4.67 ± 1.52
	72- 96	4.39	3.94	4.69	4.34 ± 0.38
	96-120	3.45	2.98	3.93	3.45 ± 0.48
	120-144	4.11	2.98	3.53	3.54 ± 0.57
	144-168	2.91	2.04	2.05	2.33 ± 0.50
	168-192	2.28	2.37	1.98	2.21 ± 0.20
	192-216	1.84	2.28	1.95	2.02 ± 0.23
	216-240	2.00	1.65	1.42	1.69 ± 0.29
	Total	43.75	38.92	50.10	44.26 ± 5.61
Urine	0- 6	0.06	0.03	0.07	0.05 ± 0.02
	6- 24	0.96	0.84	1.55	1.12 ± 0.38
	24- 48	1.35	1.00	1.75	1.37 ± 0.38
	48- 72	1.16	0.92	1.63	1.24 ± 0.36
	72- 96	1.17	0.98	1.45	1.20 ± 0.24
	96-120	1.11	0.85	1.31	1.09 ± 0.23
	120-144	1.02	0.85	1.17	1.01 ± 0.16
	144-168	0.93	0.81	1.04	0.93 ± 0.12
	168-192	0.93	0.81	0.83	0.86 ± 0.06
	192-216	0.87	0.83	0.87	0.86 ± 0.02
	216-240	0.60	0.60	0.81	0.67 ± 0.12
	Total	10.16	8.52	12.48	10.39 ± 1.99
Cage wash	0- 24	0.11	0.08	0.15	0.11 ± 0.04
	24- 48	0.16	0.08	0.17	0.14 ± 0.05
	48- 72	0.50	0.07	0.09	0.22 ± 0.24
	72- 96	0.11	0.06	0.10	0.09 ± 0.03
	96-120	0.05	0.04	0.06	0.05 ± 0.01
	120-144	0.06	0.07	0.07	0.07 ± 0.01
	144-168	0.09	0.06	0.05	0.07 ± 0.02
	168-192	0.04	0.05	0.05	0.05 ± 0.01
	192-216	0.08	0.11	0.05	0.08 ± 0.03
	216-240	0.08	NS	0.05	0.04 ± 0.04
	Total	1.28	0.62	0.84	0.91 ± 0.34
	Overall total	55.19	48.06	63.42	55.56 ± 7.69

SD Standard deviation
NS No sample

TABLE 28

Cumulative excretion of radioactivity by beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		1	2	3	
Faeces	0- 24	12.21	10.15	18.49	13.62 ± 4.34
	0- 48	19.75	14.66	25.58	20.00 ± 5.46
	0- 72	22.77	20.68	30.55	24.67 ± 5.20
	0- 96	27.16	24.62	35.24	29.01 ± 5.55
	0-120	30.61	27.60	39.17	32.46 ± 6.00
	0-144	34.72	30.58	42.70	36.00 ± 6.16
	0-168	37.63	32.62	44.75	38.33 ± 6.10
	0-192	39.91	34.99	46.73	40.54 ± 5.90
	0-216	41.75	37.27	48.68	42.57 ± 5.75
	0-240	43.75	38.92	50.10	44.26 ± 5.61
Urine	0- 6	0.06	0.03	0.07	0.05 ± 0.02
	0- 24	1.02	0.87	1.62	1.17 ± 0.40
	0- 48	2.37	1.87	3.37	2.54 ± 0.76
	0- 72	3.53	2.79	5.00	3.77 ± 1.12
	0- 96	4.70	3.77	6.45	4.97 ± 1.36
	0-120	5.81	4.62	7.76	6.06 ± 1.59
	0-144	6.83	5.47	8.93	7.08 ± 1.74
	0-168	7.76	6.28	9.97	8.00 ± 1.86
	0-192	8.69	7.09	10.80	8.86 ± 1.86
	0-216	9.56	7.92	11.67	9.72 ± 1.88
	0-240	10.16	8.52	12.48	10.39 ± 1.99
Cage wash	0- 24	0.11	0.08	0.15	0.11 ± 0.04
	0- 48	0.27	0.16	0.32	0.25 ± 0.08
	0- 72	0.77	0.23	0.41	0.47 ± 0.27
	0- 96	0.88	0.29	0.51	0.56 ± 0.30
	0-120	0.93	0.33	0.57	0.61 ± 0.30
	0-144	0.99	0.40	0.64	0.68 ± 0.30
	0-168	1.08	0.46	0.69	0.74 ± 0.31
	0-192	1.12	0.51	0.74	0.79 ± 0.31
	0-216	1.20	0.62	0.79	0.87 ± 0.30
	0-240	1.28	0.62	0.84	0.91 ± 0.34
	Overall total	55.19	48.06	63.42	55.56 ± 7.69

SD Standard deviation

TABLE 29

The excretion of radioactivity by beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		4	5	6	
Faeces	0 - 24	5.17	4.33	12.36	7.29 ± 4.41
	24 - 48	2.64	10.28	3.97	5.63 ± 4.06
	48 - 72	3.08	3.96	4.79	3.94 ± 0.86
	72 - 96	3.99	5.20	5.50	4.90 ± 0.80
	96 -120	2.22	3.40	4.20	3.27 ± 1.00
	120 -144	3.32	3.87	2.97	3.39 ± 0.45
	144 -168	1.87	2.19	2.46	2.17 ± 0.30
	168 -192	2.03	3.01	2.02	2.35 ± 0.57
	192 -216	1.50	2.34	2.60	2.15 ± 0.57
	216 -240	2.56	2.76	2.18	2.50 ± 0.29
	Total	28.38	41.34	43.05	37.59 ± 8.02
Urine	0 - 6	0.27	0.32	0.28	0.29 ± 0.03
	6 - 24	1.02	1.14	1.15	1.10 ± 0.07
	24 - 48	0.96	0.94	1.27	1.06 ± 0.19
	48 - 72	0.98	1.18	1.31	1.16 ± 0.17
	72 - 96	1.08	1.18	1.32	1.19 ± 0.12
	96 -120	1.11	1.05	1.22	1.13 ± 0.09
	120 -144	1.09	1.10	1.23	1.14 ± 0.08
	144 -168	0.95	0.98	1.03	0.99 ± 0.04
	168 -192	0.87	2.13	0.96	1.32 ± 0.70
	192 -216	0.27	0.47	0.88	0.54 ± 0.31
	216 -240	0.82	0.80	0.79	0.80 ± 0.02
	Total	9.42	11.29	11.44	10.72 ± 1.13
Cage wash*	0 - 0.5	10.46	NS	3.01	4.49 ± 5.38
	0.5- 1	5.36	1.58	0.51	2.48 ± 2.55
	1 - 1.5	NS	NS	0.65	0.22 ± 0.38
	1.5- 24	0.08	0.05	0.19	0.11 ± 0.07
	24 - 48	0.12	0.13	0.18	0.14 ± 0.03
	48 - 72	0.14	0.11	0.13	0.13 ± 0.02
	72 - 96	0.07	0.09	0.09	0.08 ± 0.01
	96 -120	0.06	0.08	0.10	0.08 ± 0.02
	120 -144	0.05	0.06	0.10	0.07 ± 0.03
	144 -168	0.06	0.06	0.09	0.07 ± 0.02
	168 -192	0.04	0.05	0.08	0.06 ± 0.02
	192 -216	0.05	0.05	0.10	0.07 ± 0.03
	216 -240	0.05	0.07	0.07	0.06 ± 0.01
	Total	16.54	2.33	5.30	8.06 ± 7.50
Overall total		54.34	54.96	59.79	56.36 ± 2.98

* 0-1.5 hour data includes vomited portion of dose for each dog
SD Standard deviation
NS No sample

TABLE 30

Cumulative excretion of radioactivity by beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		4	5	6	
Faeces	0- 24	5.17	4.33	12.36	7.29 ± 4.41
	0- 48	7.81	14.61	16.33	12.92 ± 4.51
	0- 72	10.89	18.57	21.12	16.86 ± 5.33
	0- 96	14.88	23.77	26.62	21.76 ± 6.12
	0-120	17.10	27.17	30.82	25.03 ± 7.11
	0-144	20.42	31.04	33.79	28.42 ± 7.06
	0-168	22.29	33.23	36.25	30.59 ± 7.34
	0-192	24.32	36.24	38.27	32.94 ± 7.54
	0-216	25.82	38.58	40.87	35.09 ± 8.11
	0-240	28.38	41.34	43.05	37.59 ± 8.02
Urine	0- 6	0.27	0.32	0.28	0.29 ± 0.03
	0- 24	1.29	1.46	1.43	1.39 ± 0.09
	0- 48	2.25	2.40	2.70	2.45 ± 0.23
	0- 72	3.23	3.58	4.01	3.61 ± 0.39
	0- 96	4.31	4.76	5.33	4.80 ± 0.51
	0-120	5.42	5.81	6.55	5.93 ± 0.57
	0-144	6.51	6.91	7.78	7.07 ± 0.65
	0-168	7.46	7.89	8.81	8.05 ± 0.69
	0-192	8.33	10.02	9.77	9.37 ± 0.91
	0-216	8.60	10.49	10.65	9.91 ± 1.14
	0-240	9.42	11.29	11.44	10.72 ± 1.13
Cage wash*	0- 0.5	10.46	0.00	3.01	4.49 ± 5.38
	0- 1	15.82	1.58	3.52	6.97 ± 7.72
	0- 1.5	15.82	1.58	4.17	7.19 ± 7.59
	0- 24	15.90	1.63	4.36	7.30 ± 7.57
	0- 48	16.02	1.76	4.54	7.44 ± 7.56
	0- 72	16.16	1.87	4.67	7.57 ± 7.57
	0- 96	16.23	1.96	4.76	7.65 ± 7.56
	0-120	16.29	2.04	4.86	7.73 ± 7.55
	0-144	16.34	2.10	4.96	7.80 ± 7.53
	0-168	16.40	2.16	5.05	7.87 ± 7.53
	0-192	16.44	2.21	5.13	7.93 ± 7.52
	0-216	16.49	2.26	5.23	7.99 ± 7.51
	0-240	16.54	2.33	5.30	8.06 ± 7.50
	Overall total	54.34	54.96	59.79	56.36 ± 2.98

* 0-1.5 hour data includes vomited portion of dose for each dog

SD Standard deviation

TABLE 31

The excretion of radioactivity by beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		1	2	3	
Faeces	0 - 24	12.69	31.43	8.79	17.64 ± 12.10
	24 - 48	6.48	1.61	5.29	4.46 ± 2.54
	48 - 72	4.24	0.85	2.73	2.61 ± 1.70
	72 - 96	2.37	1.36	4.15	2.63 ± 1.41
	96 -120	1.91	0.91	2.39	1.74 ± 0.76
	120 -144	1.52	0.62	2.14	1.43 ± 0.76
	144 -168	1.45	0.98	2.22	1.55 ± 0.63
	168 -192	2.57	0.68	1.97	1.74 ± 0.97
	192 -216	0.76	0.58	1.85	1.06 ± 0.69
	216 -240	1.81	0.74	2.06	1.54 ± 0.70
	Total	35.80	39.76	33.59	36.38 ± 3.13
Urine	0 - 6	0.07	0.03	0.04	0.05 ± 0.02
	6 - 24	0.69	0.43	0.75	0.62 ± 0.17
	24 - 48	0.70	0.30	0.72	0.57 ± 0.24
	48 - 72	0.69	0.32	0.74	0.58 ± 0.23
	72 - 96	0.62	0.31	0.76	0.56 ± 0.23
	96 -120	0.65	0.30	0.73	0.56 ± 0.23
	120 -144	0.59	0.30	0.66	0.52 ± 0.19
	144 -168	0.58	0.28	0.62	0.49 ± 0.19
	168 -192	0.58	0.27	0.63	0.49 ± 0.20
	192 -216	0.57	0.24	0.50	0.44 ± 0.17
	216 -240	0.50	0.23	0.63	0.45 ± 0.20
	Total	6.24	3.01	6.78	5.34 ± 2.04
Cage wash*	0 - 0.5	4.62	16.23	NS	6.95 ± 8.36
	0.5- 1	NS	0.55	12.66	4.40 ± 7.16
	1 - 1.5	3.13	NS	NS	1.04 ± 1.81
	1.5- 24	0.14	0.17	0.08	0.13 ± 0.05
	24 - 48	0.06	0.09	0.12	0.09 ± 0.03
	48 - 72	0.05	0.06	0.07	0.06 ± 0.01
	72 - 96	0.05	0.05	0.05	0.05 ± 0.00
	96 -120	0.04	0.02	0.05	0.04 ± 0.02
	120 -144	0.04	0.03	0.05	0.04 ± 0.01
	144 -168	0.04	0.02	0.04	0.03 ± 0.01
	168 -192	0.05	0.02	0.05	0.04 ± 0.02
	192 -216	0.04	0.03	0.07	0.05 ± 0.02
	216 -240	0.04	0.02	0.05	0.04 ± 0.02
	Total	8.30	17.29	13.29	12.96 ± 4.50
	Overall total	50.34	60.06	53.66	54.69 ± 4.94

* 0-1.5 hour data includes vomited portion of dose for each dog
SD Standard deviation
NS No sample

TABLE 32

Cumulative excretion of radioactivity by beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		1	2	3	
Faeces	0 - 24	12.69	31.43	8.79	17.64 ± 12.10
	0 - 48	19.17	33.04	14.08	22.10 ± 9.81
	0 - 72	23.41	33.89	16.81	24.70 ± 8.61
	0 - 96	25.78	35.25	20.96	27.33 ± 7.27
	0 -120	27.69	36.16	23.35	29.07 ± 6.52
	0 -144	29.21	36.78	25.49	30.49 ± 5.75
	0 -168	30.66	37.76	27.71	32.04 ± 5.17
	0 -192	33.23	38.44	29.68	33.78 ± 4.41
	0 -216	33.99	39.02	31.53	34.85 ± 3.82
	0 -240	35.80	39.76	33.59	36.38 ± 3.13
Urine	0 - 6	0.07	0.03	0.04	0.05 ± 0.02
	0 - 24	0.76	0.46	0.79	0.67 ± 0.18
	0 - 48	1.46	0.76	1.51	1.24 ± 0.42
	0 - 72	2.15	1.08	2.25	1.83 ± 0.65
	0 - 96	2.77	1.39	3.01	2.39 ± 0.87
	0 -120	3.42	1.69	3.74	2.95 ± 1.10
	0 -144	4.01	1.99	4.40	3.47 ± 1.29
	0 -168	4.59	2.27	5.02	3.96 ± 1.48
	0 -192	5.17	2.54	5.65	4.45 ± 1.67
	0 -216	5.74	2.78	6.15	4.89 ± 1.84
	0 -240	6.24	3.01	6.78	5.34 ± 2.04
Cage wash*	0 - 0.5	4.62	16.23	0.00	6.95 ± 8.36
	0 - 1	4.62	16.78	12.66	11.35 ± 6.18
	0 - 1.5	7.75	16.78	12.66	12.40 ± 4.52
	1.5- 24	7.89	16.95	12.74	12.53 ± 4.53
	0 - 48	7.95	17.04	12.86	12.62 ± 4.55
	0 - 72	8.00	17.10	12.93	12.68 ± 4.56
	0 - 96	8.05	17.15	12.98	12.73 ± 4.56
	0 -120	8.09	17.17	13.03	12.76 ± 4.55
	0 -144	8.13	17.20	13.08	12.80 ± 4.54
	0 -168	8.17	17.22	13.12	12.84 ± 4.53
	0 -192	8.22	17.24	13.17	12.88 ± 4.52
	0 -216	8.26	17.27	13.24	12.92 ± 4.51
	0 -240	8.30	17.29	13.29	12.96 ± 4.50
	Overall total	50.34	60.06	53.66	54.69 ± 4.94

* 0-1.5 hour data includes vomited portion of dose for each dog

SD Standard deviation

TABLE 33

The excretion of radioactivity by beagle dogs following the intravenous administration of a single dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		3	4	6	
Faeces	0- 24	3.07	4.38	4.44	3.96 ± 0.77
	24- 48	5.99	9.14	7.27	7.47 ± 1.58
	48- 72	5.08	5.61	6.84	5.84 ± 0.90
	72- 96	7.63	5.03	6.25	6.30 ± 1.30
	96-120	3.49	4.06	4.18	3.91 ± 0.37
	120-144	3.80	3.10	3.88	3.59 ± 0.43
	144-168	3.13	3.09	3.87	3.36 ± 0.44
	168-192	4.17	1.93	2.90	3.00 ± 1.12
	192-216	2.61	2.13	1.93	2.22 ± 0.35
	216-240	1.46	1.54	1.58	1.53 ± 0.06
	Total	40.43	40.01	43.14	41.19 ± 1.70
Urine	0- 6	NS	0.36	0.51	0.29 ± 0.26
	6- 24	2.55	2.05	2.59	2.40 ± 0.30
	24- 48	1.48	2.46	3.41	2.45 ± 0.97
	48- 72	3.04	2.54	2.98	2.85 ± 0.27
	72- 96	2.28	2.08	2.23	2.20 ± 0.10
	96-120	1.80	1.94	1.91	1.88 ± 0.07
	120-144	1.46	1.67	1.51	1.55 ± 0.11
	144-168	1.50	1.55	1.34	1.46 ± 0.11
	168-192	1.33	1.18	0.92	1.14 ± 0.21
	192-216	0.97	0.91	1.07	0.98 ± 0.08
	216-240	0.87	0.76	0.93	0.85 ± 0.09
	Total	17.28	17.50	19.40	18.06 ± 1.17
Cage wash	0- 24	0.05	0.03	0.08	0.05 ± 0.03
	24- 48	0.08	0.06	0.10	0.08 ± 0.02
	48- 72	0.04	0.05	0.09	0.06 ± 0.03
	72- 96	0.07	0.04	0.07	0.06 ± 0.02
	96-120	0.04	0.03	0.07	0.05 ± 0.02
	120-144	0.04	0.04	0.09	0.06 ± 0.03
	144-168	0.03	0.03	0.05	0.04 ± 0.01
	168-192	0.02	0.02	0.02	0.02 ± 0.00
	192-216	0.02	0.01	0.02	0.02 ± 0.01
	216-240	0.02	0.02	ND	0.01 ± 0.01
	Total	0.41	0.33	0.59	0.44 ± 0.13
	Overall total	58.12	57.84	63.13	59.70 ± 2.98

SD Standard deviation
NS No sample
ND Not detected

TABLE 34

Cumulative excretion of radioactivity by beagle dogs following the intravenous administration of a single dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Dog number			Mean ± SD
		3	4	6	
Faeces	0- 24	3.07	4.38	4.44	3.96 ± 0.77
	0- 48	9.06	13.52	11.71	11.43 ± 2.24
	0- 72	14.14	19.13	18.55	17.27 ± 2.73
	0- 96	21.77	24.16	24.80	23.58 ± 1.60
	0-120	25.26	28.22	28.98	27.49 ± 1.97
	0-144	29.06	31.32	32.86	31.08 ± 1.91
	0-168	32.19	34.41	36.73	34.44 ± 2.27
	0-192	36.36	36.34	39.63	37.44 ± 1.89
	0-216	38.97	38.47	41.56	39.67 ± 1.66
	0-240	40.43	40.01	43.14	41.19 ± 1.70
Urine	0- 6	0.00	0.36	0.51	0.29 ± 0.26
	0- 24	2.55	2.41	3.10	2.69 ± 0.36
	0- 48	4.03	4.87	6.51	5.14 ± 1.26
	0- 72	7.07	7.41	9.49	7.99 ± 1.31
	0- 96	9.35	9.49	11.72	10.19 ± 1.33
	0-120	11.15	11.43	13.63	12.07 ± 1.36
	0-144	12.61	13.10	15.14	13.62 ± 1.34
	0-168	14.11	14.65	16.48	15.08 ± 1.24
	0-192	15.44	15.83	17.40	16.22 ± 1.04
	0-216	16.41	16.74	18.47	17.21 ± 1.11
	0-240	17.28	17.50	19.40	18.06 ± 1.17
Cage wash	0- 24	0.05	0.03	0.08	0.05 ± 0.03
	0- 48	0.13	0.09	0.18	0.13 ± 0.05
	0- 72	0.17	0.14	0.27	0.19 ± 0.07
	0- 96	0.24	0.18	0.34	0.25 ± 0.08
	0-120	0.28	0.21	0.41	0.30 ± 0.10
	0-144	0.32	0.25	0.50	0.36 ± 0.13
	0-168	0.35	0.28	0.55	0.39 ± 0.14
	0-192	0.37	0.30	0.57	0.41 ± 0.14
	0-216	0.39	0.31	0.59	0.43 ± 0.14
	0-240	0.41	0.33	0.59	0.44 ± 0.13
	Overall total	58.12	57.84	63.13	59.70 ± 2.98

SD Standard deviation

TABLE 35

The excretion of radioactivity by rhesus monkeys following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Monkey number		Mean
		J625	H179	
Faeces	0- 6	0.79	0.04	0.42
	6- 24	6.60	20.01	13.31
	24- 48	11.72	10.47	11.10
	48- 72	8.55	7.37	7.96
	72- 96	9.31	4.19	6.75
	96-120	5.58	3.92	4.75
	120-144	3.96	6.08	5.02
	144-168	2.64	2.11	2.38
	168-192	1.97	1.69	1.83
	192-216	1.56	1.35	1.46
	216-240	1.06	0.96	1.01
	Total	53.74	58.19	55.97
Urine	0- 6	1.76	1.19	1.48
	6- 24	5.21	3.25	4.23
	24- 48	5.51	2.95	4.23
	48- 72	3.68	2.44	3.06
	72- 96	2.32	1.23	1.78
	96-120	1.97	2.15	2.06
	120-144	1.40	1.19	1.30
	144-168	1.00	0.92	0.96
	168-192	0.69	0.84	0.77
	192-216	0.59	0.69	0.64
	216-240	0.39	0.11	0.25
	Total	24.52	16.96	20.74
Cage wash	0- 24	0.09	0.20	0.15
	24- 48	0.10	0.15	0.13
	48- 72	0.16	0.12	0.14
	72- 96	0.08	0.11	0.10
	96-120	0.07	0.46	0.27
	120-144	0.08	0.09	0.09
	144-168	0.04	0.04	0.04
	168-192	0.05	0.05	0.05
	192-216	0.04	0.04	0.04
	216-240	0.02	0.03	0.03
	Total	0.73	1.29	2.02
Cage debris	0-240	0.59	3.05	1.82
	Total recovery	79.58	79.49	79.54

TABLE 36

Cumulative excretion of radioactivity by rhesus monkeys following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Results are expressed as % administered radioactivity

Sample	Time (hrs)	Monkey number		Mean
		J625	H179	
Faeces	0- 6	0.79	0.04	0.42
	0- 24	7.39	20.05	13.72
	0- 48	19.11	30.52	24.82
	0- 72	27.66	37.89	32.78
	0- 96	36.97	42.08	39.53
	0-120	42.55	46.00	44.28
	0-144	46.51	52.08	49.30
	0-168	49.15	54.19	51.67
	0-192	51.12	55.88	53.50
	0-216	52.68	57.23	54.96
	0-240	53.74	58.19	55.97
Urine	0- 6	1.76	1.19	1.48
	0- 24	6.97	4.44	5.71
	0- 48	12.48	7.39	9.94
	0- 72	16.16	9.83	13.00
	0- 96	18.48	11.06	14.77
	0-120	20.45	13.21	16.83
	0-144	21.85	14.40	18.13
	0-168	22.85	15.32	19.09
	0-192	23.54	16.16	19.85
	0-216	24.13	16.85	20.49
	0-240	24.52	16.96	20.74
Cage wash	0- 24	0.09	0.20	0.15
	0- 48	0.19	0.35	0.27
	0- 72	0.35	0.47	0.41
	0- 96	0.43	0.58	0.51
	0-120	0.50	1.04	0.77
	0-144	0.58	1.13	0.86
	0-168	0.62	1.17	0.90
	0-192	0.67	1.22	0.95
	0-216	0.71	1.26	0.99
	0-240	0.73	1.29	1.01
Cage debris	0-240	0.59	3.05	1.82
	Total recovery	79.58	79.49	79.54

FIGURE 1

Concentrations of radioactivity in the plasma of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Concentration is expressed as µg equivalents WR 238605 free base/ml plasma

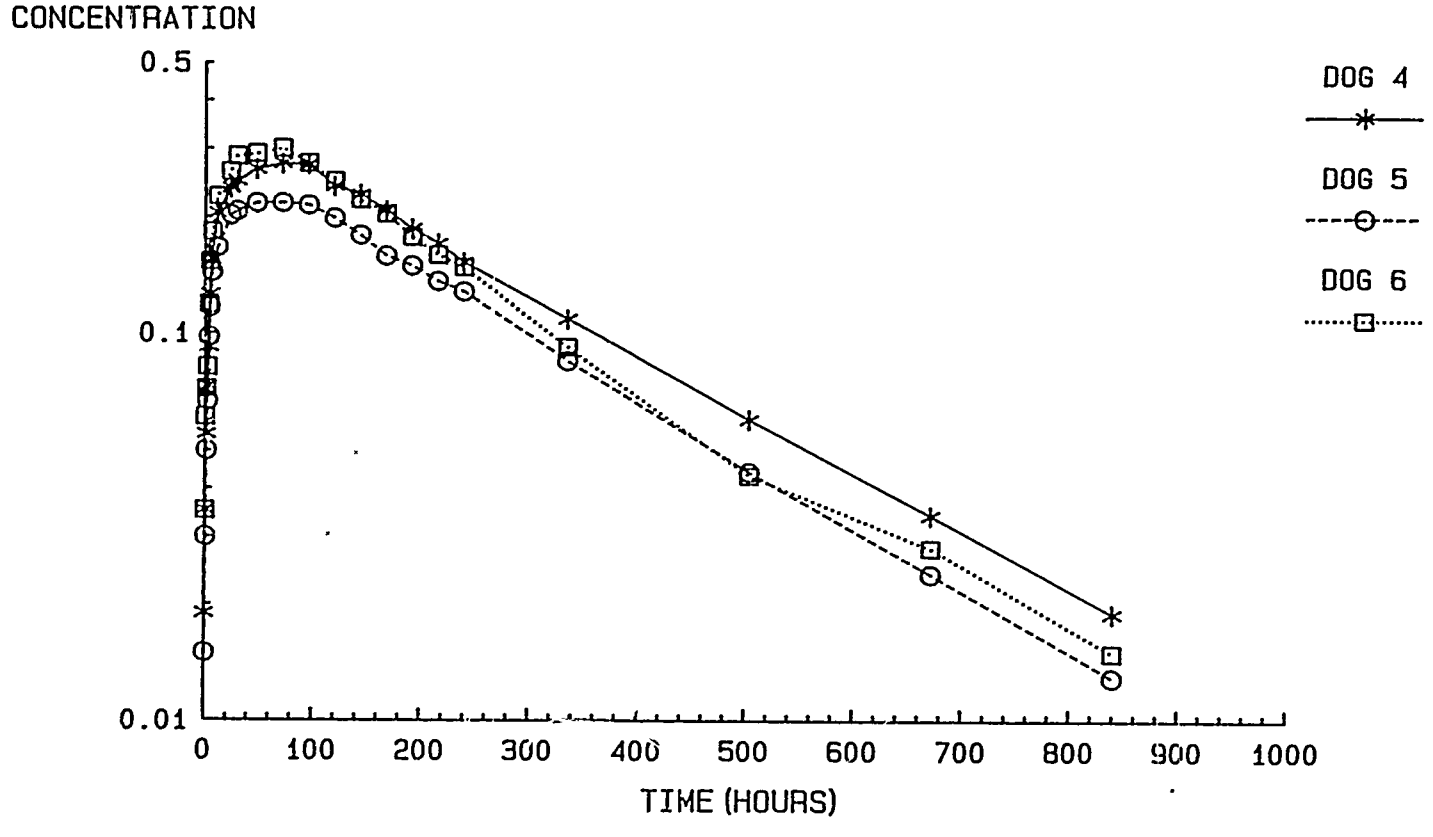


FIGURE 2

Concentrations of WR 238605 in the plasma of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma

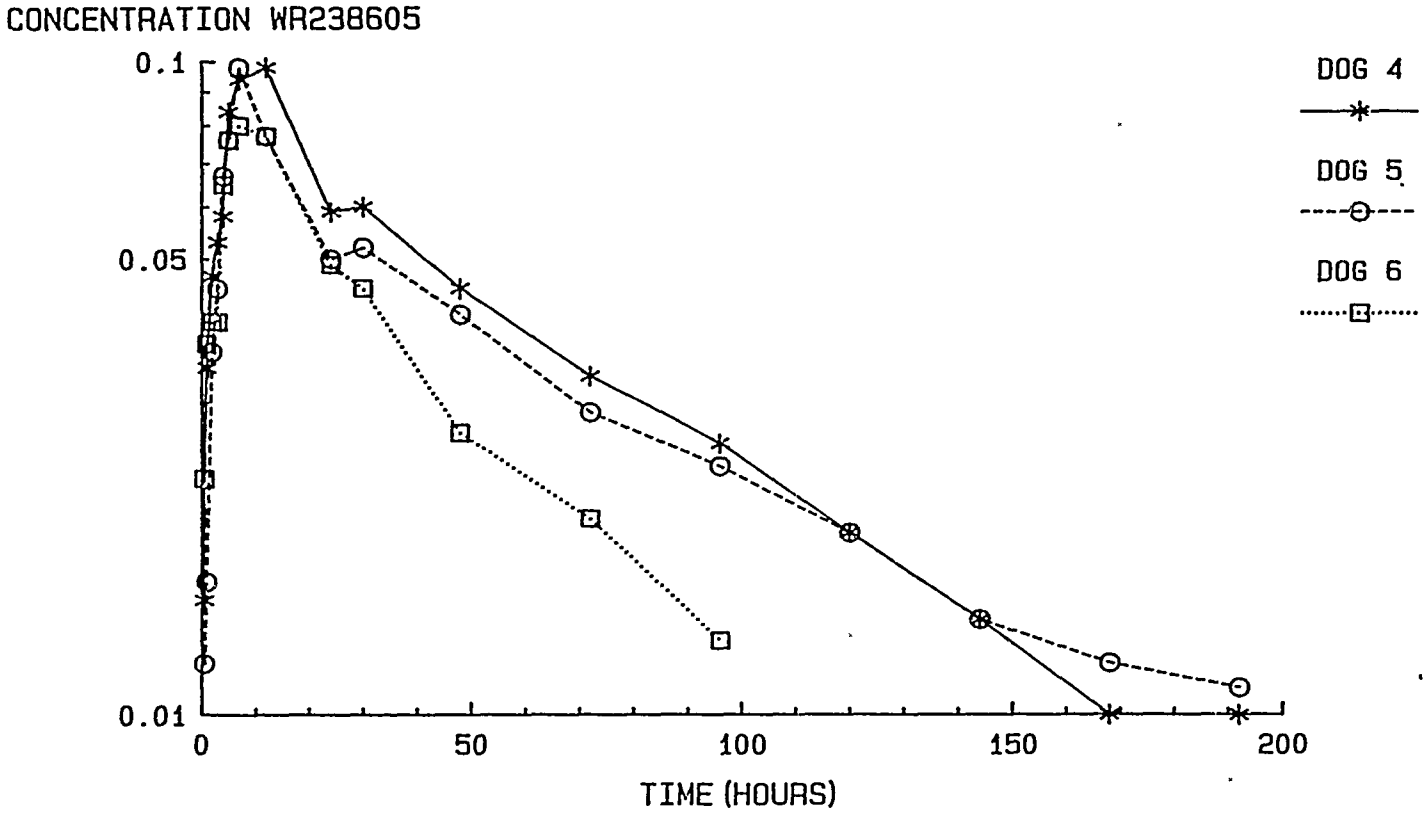


FIGURE 3

Concentrations of radioactivity in the whole-blood of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml blood

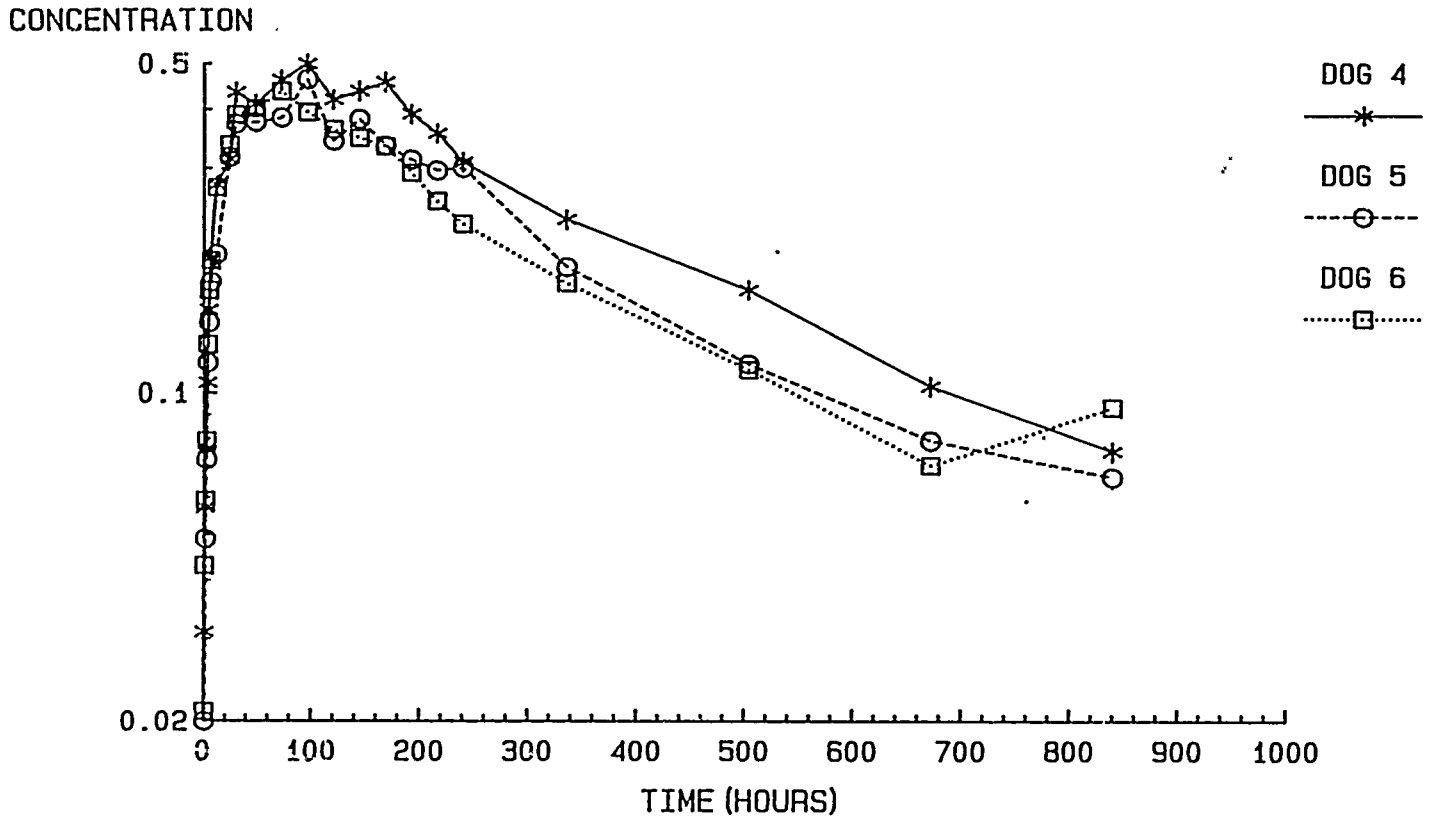


FIGURE 4

Mean concentrations of radioactivity in whole-blood and plasma and of WR 238605 in plasma of three beagle dogs following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma or, in the case of radioactivity measurements, µg equivalents WR 238605 free base/ml of whole-blood or plasma

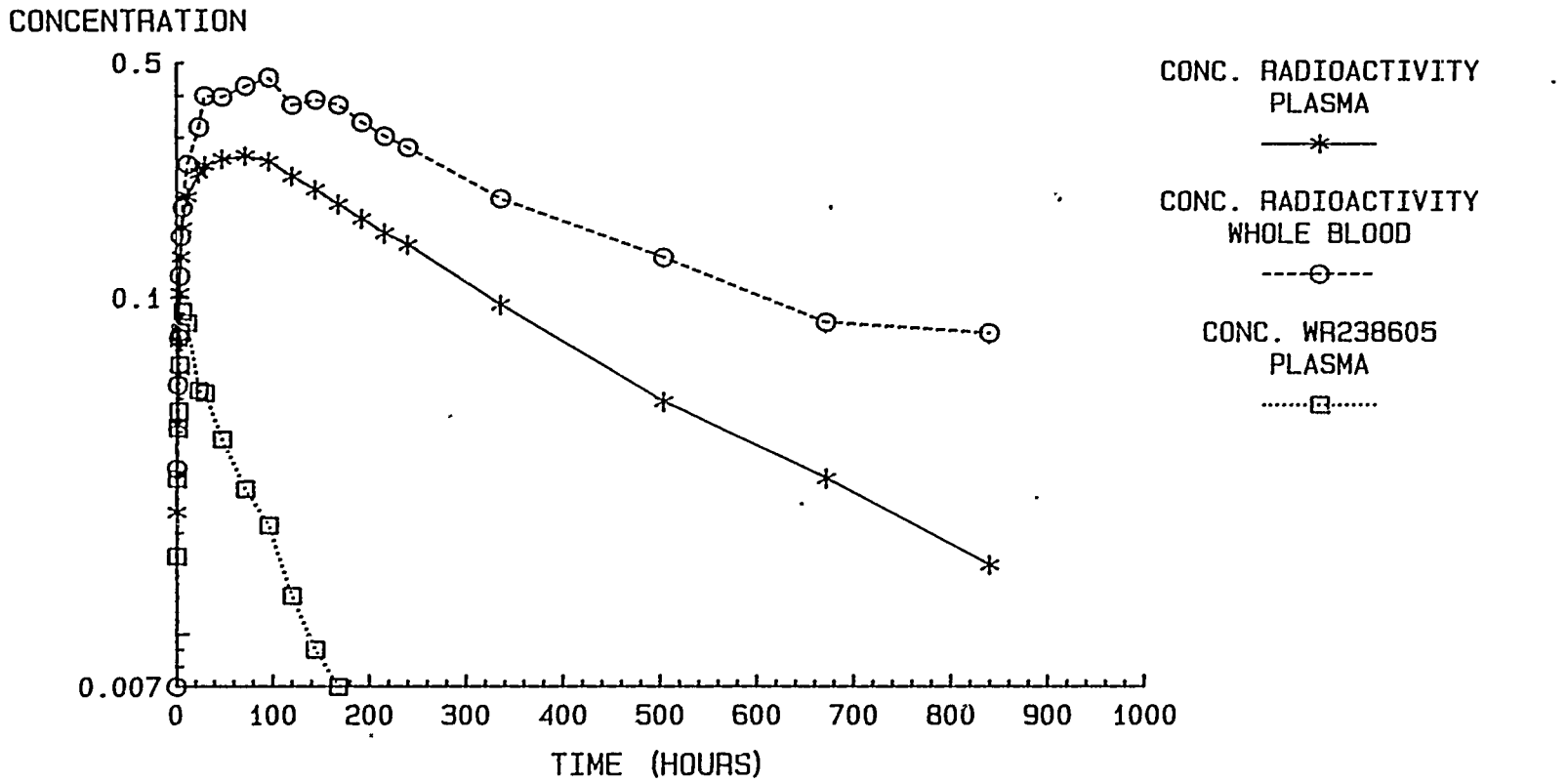


FIGURE 5

Concentrations of radioactivity in the plasma of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml plasma

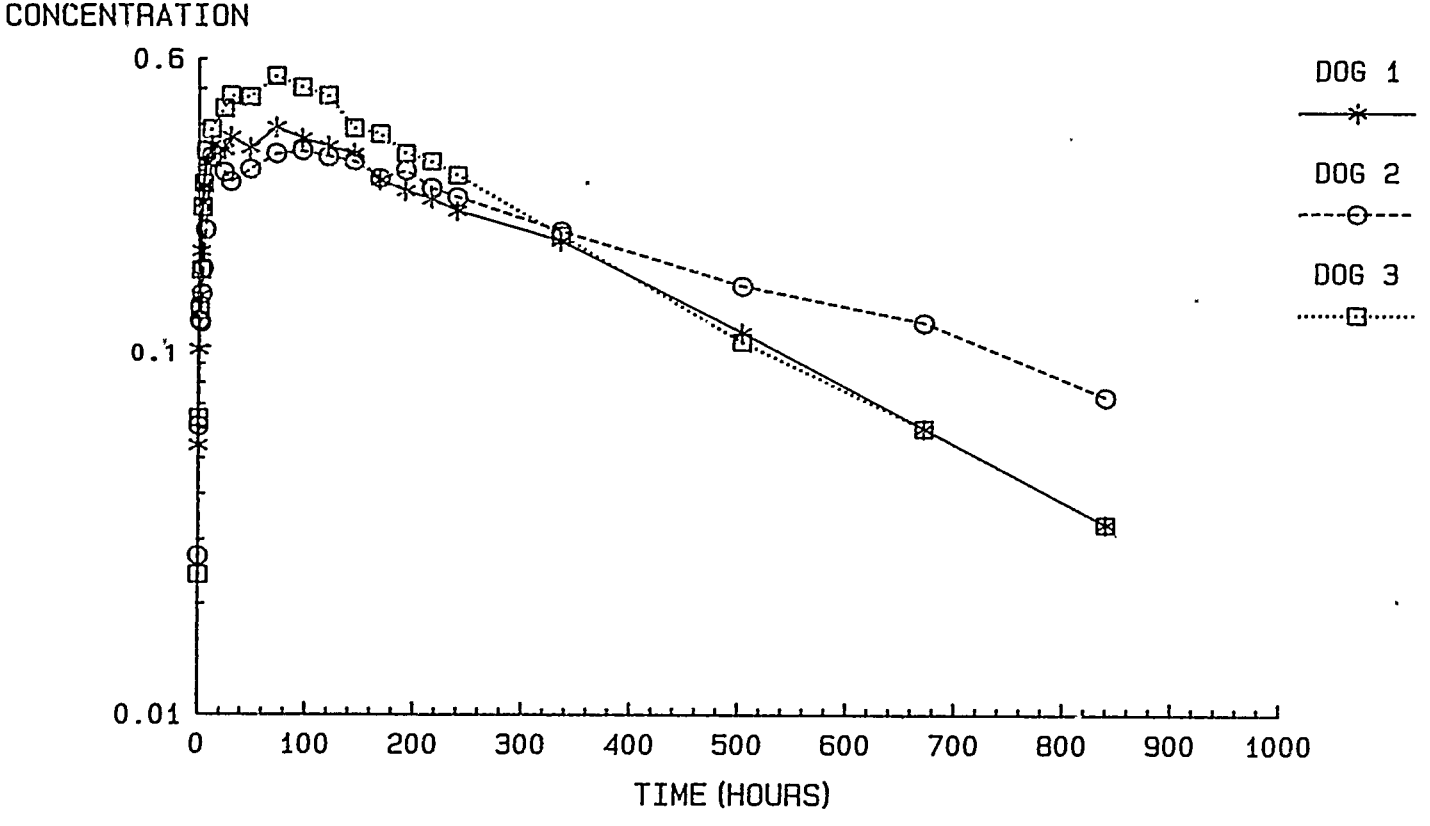


FIGURE 6

Concentrations of WR 238605 in the plasma of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma

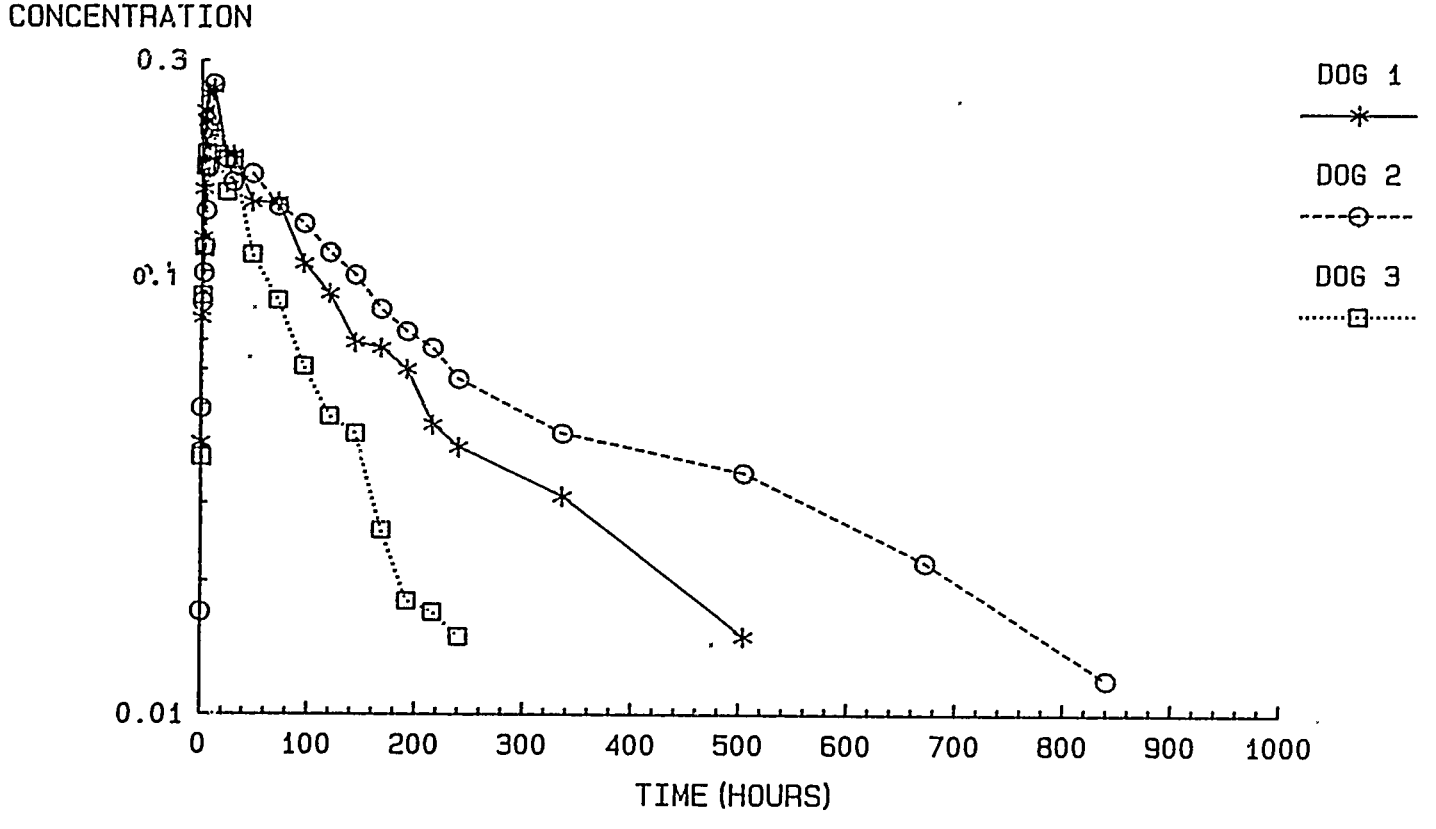


FIGURE 7

Concentrations of radioactivity in the whole-blood of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml whole-blood

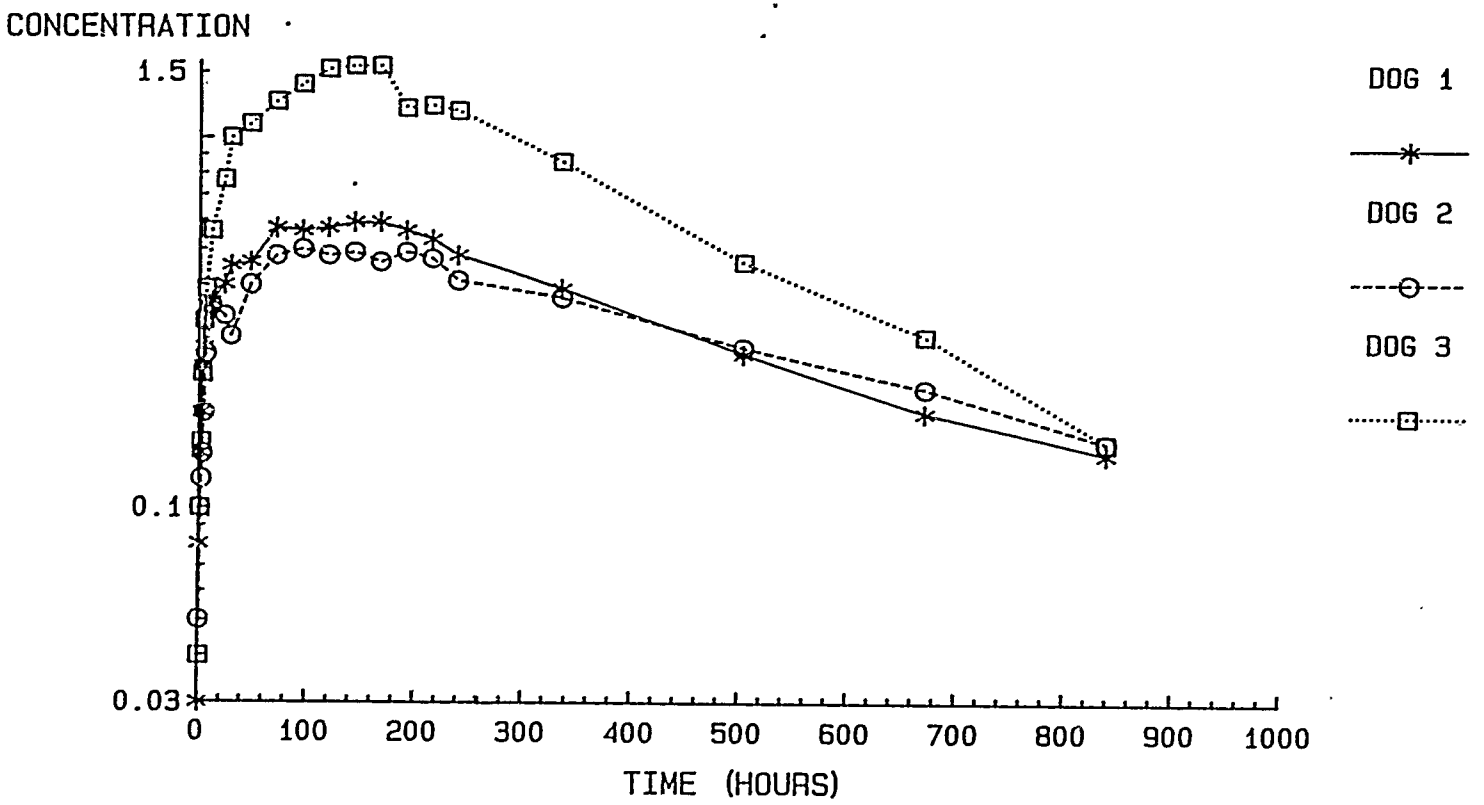


FIGURE 8

Mean concentrations of radioactivity in whole-blood and plasma and of WR 238605 in plasma of three beagle dogs following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml or as µg equivalents of WR 238605 free base/ml (radioactivity)

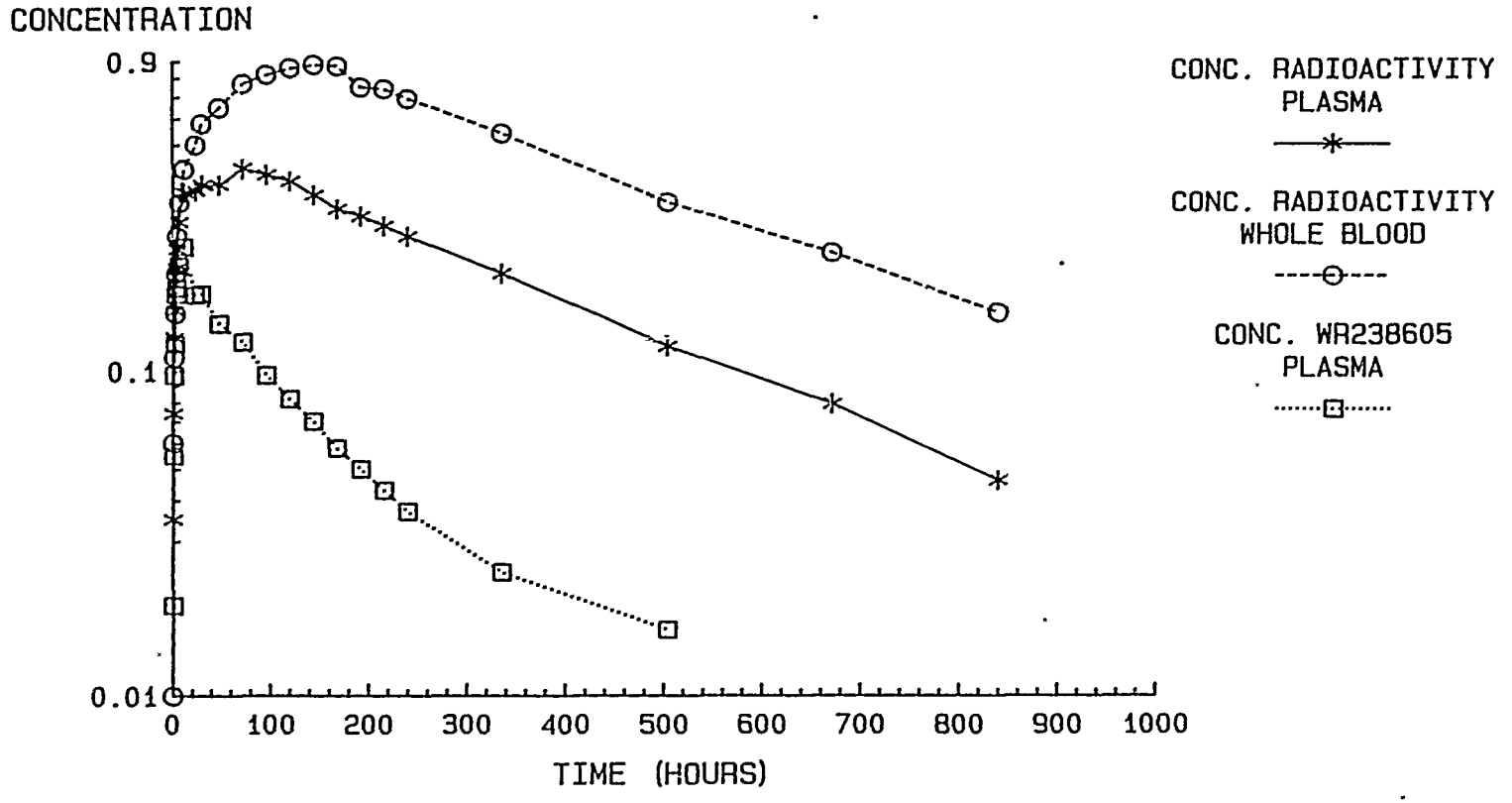


FIGURE 9

Concentrations of radioactivity in the plasma of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml plasma

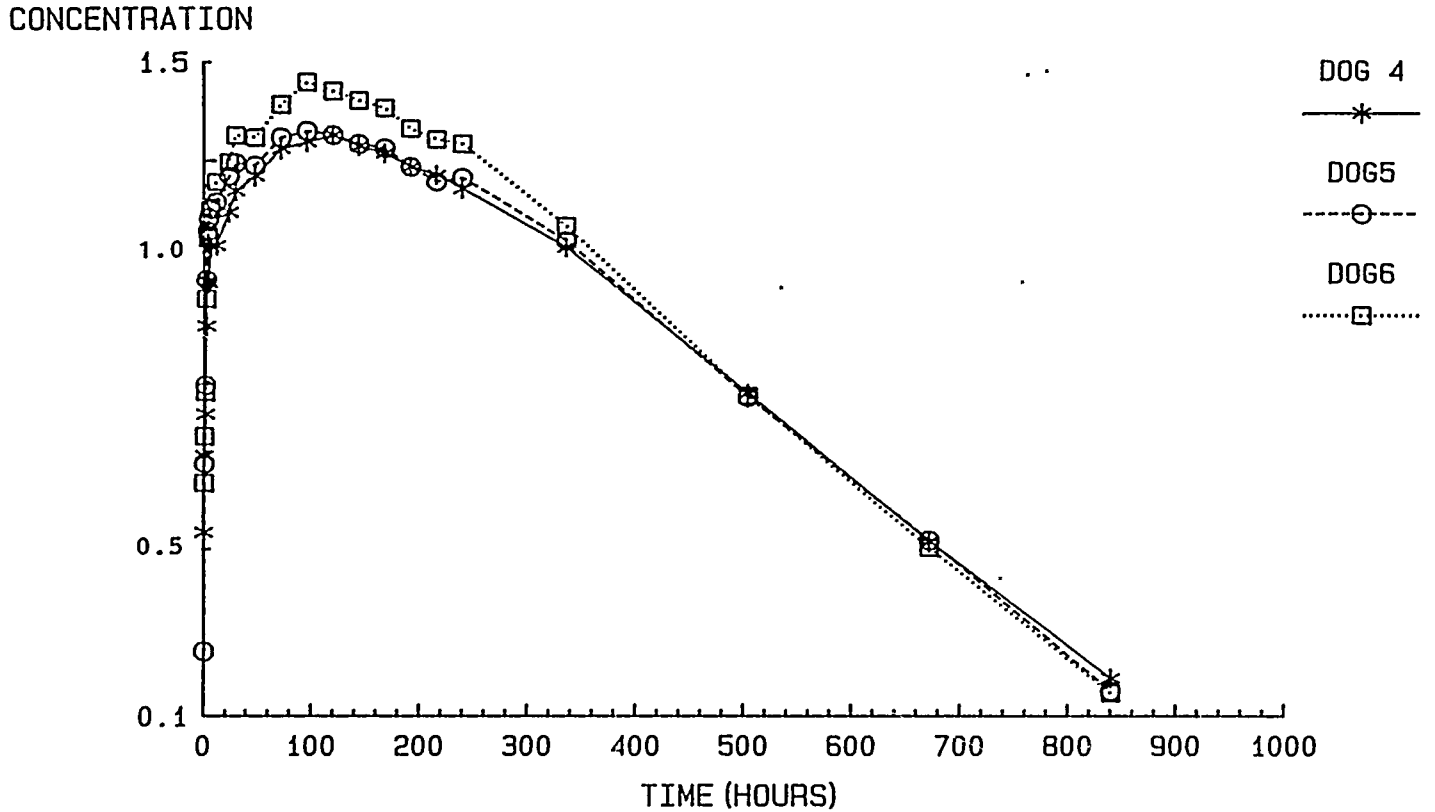


FIGURE 10

Concentrations of WR 238605 in the plasma of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma

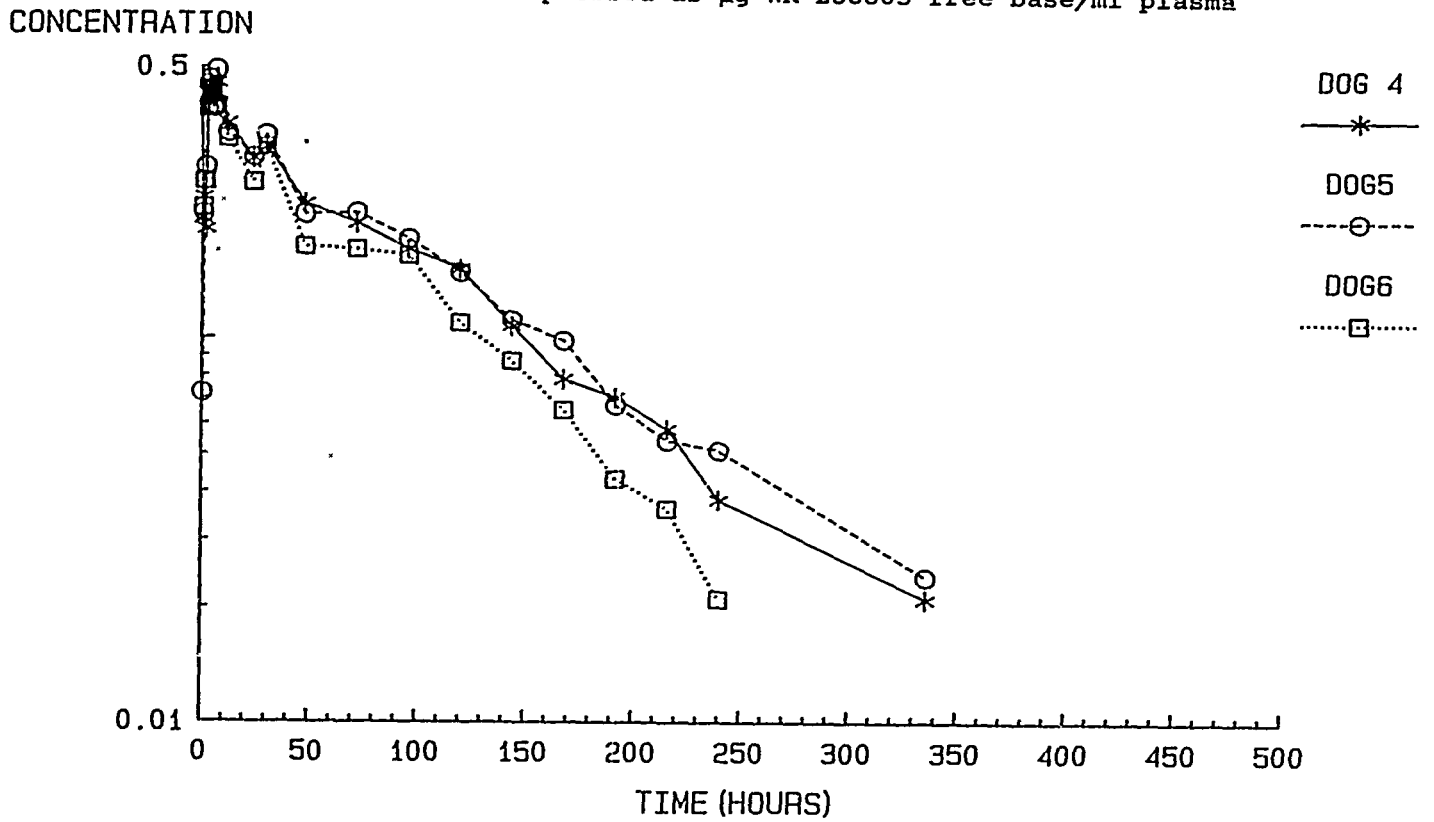


FIGURE 11

Concentrations of radioactivity in the whole-blood of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml whole-blood

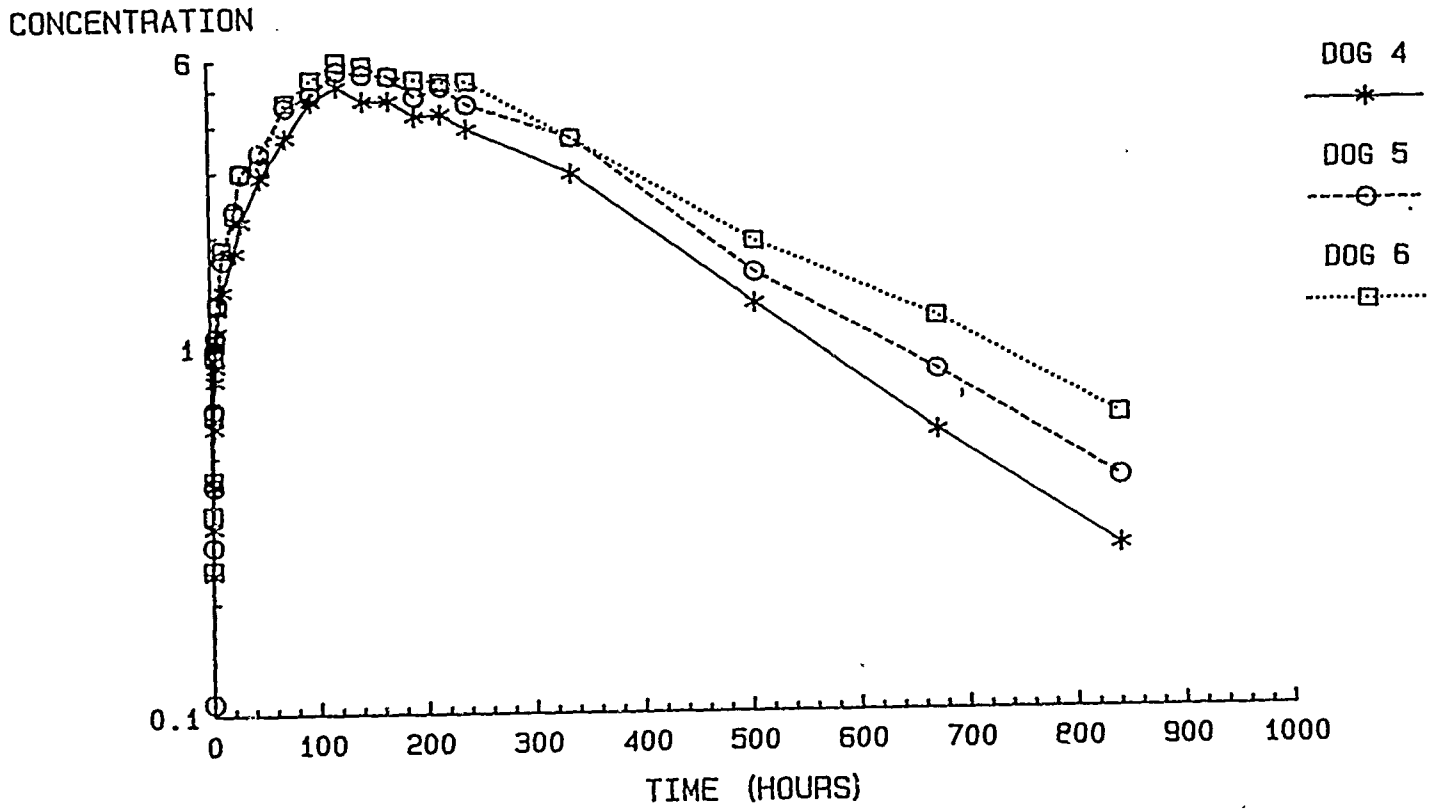


FIGURE 12

Mean concentrations of radioactivity in whole-blood and plasma and of WR 238605 in plasma of three beagle dogs following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma or, as µg equivalents WR 238605 free base/ml blood or plasma (radioactivity)

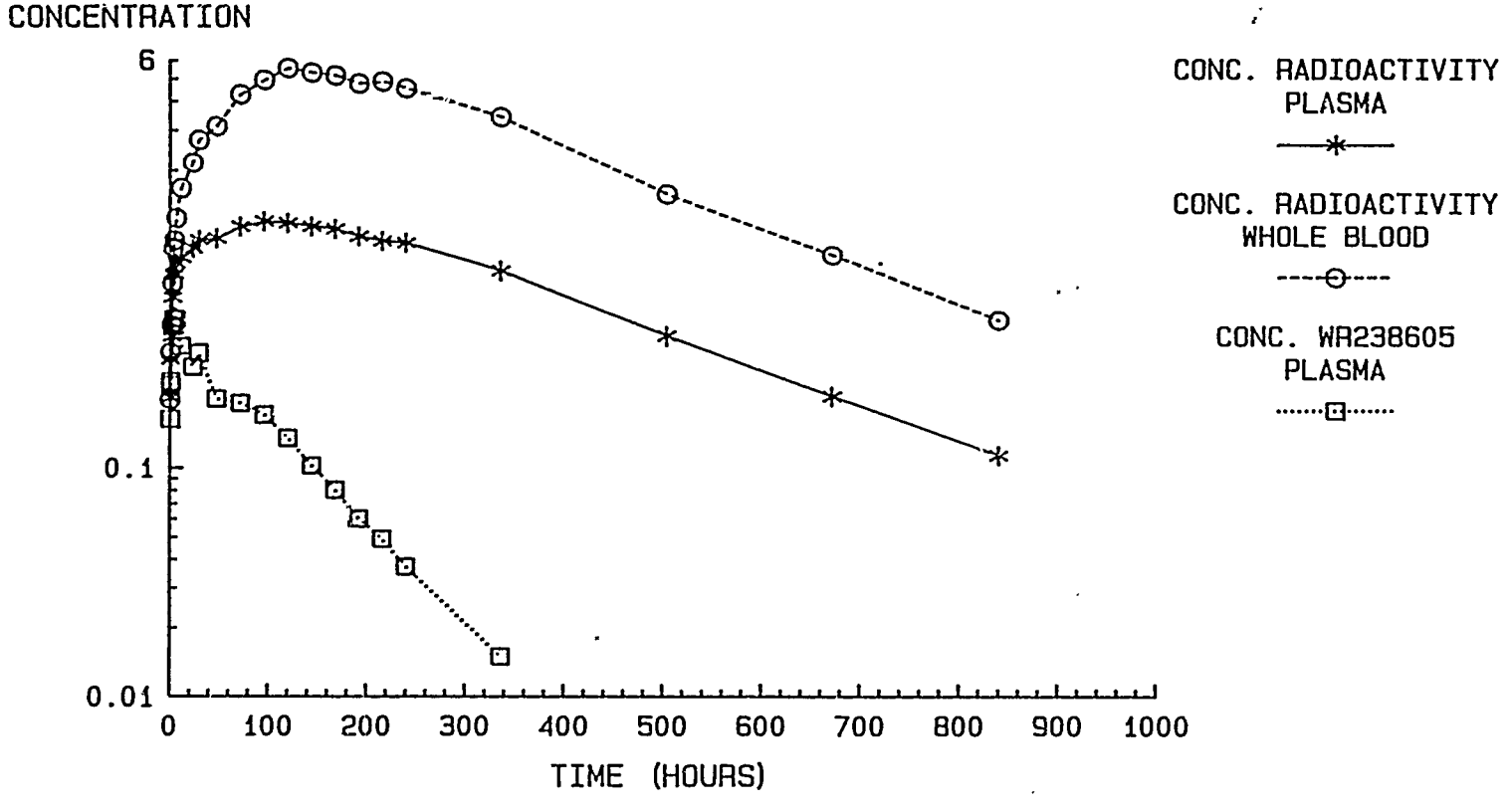


FIGURE 13

Concentrations of radioactivity in the plasma of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml plasma

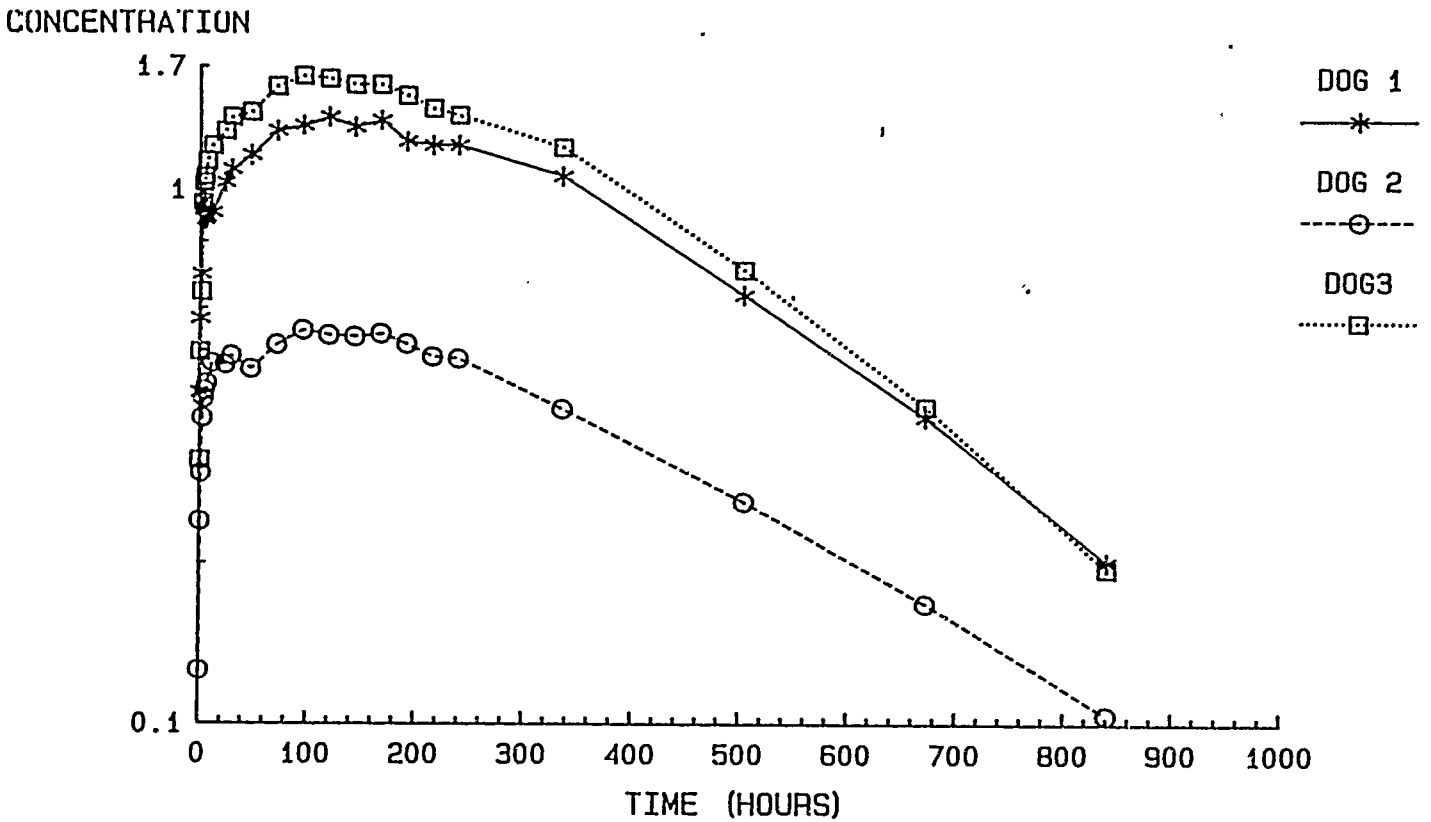


FIGURE 14

Concentrations of WR 238605 in the plasma of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma

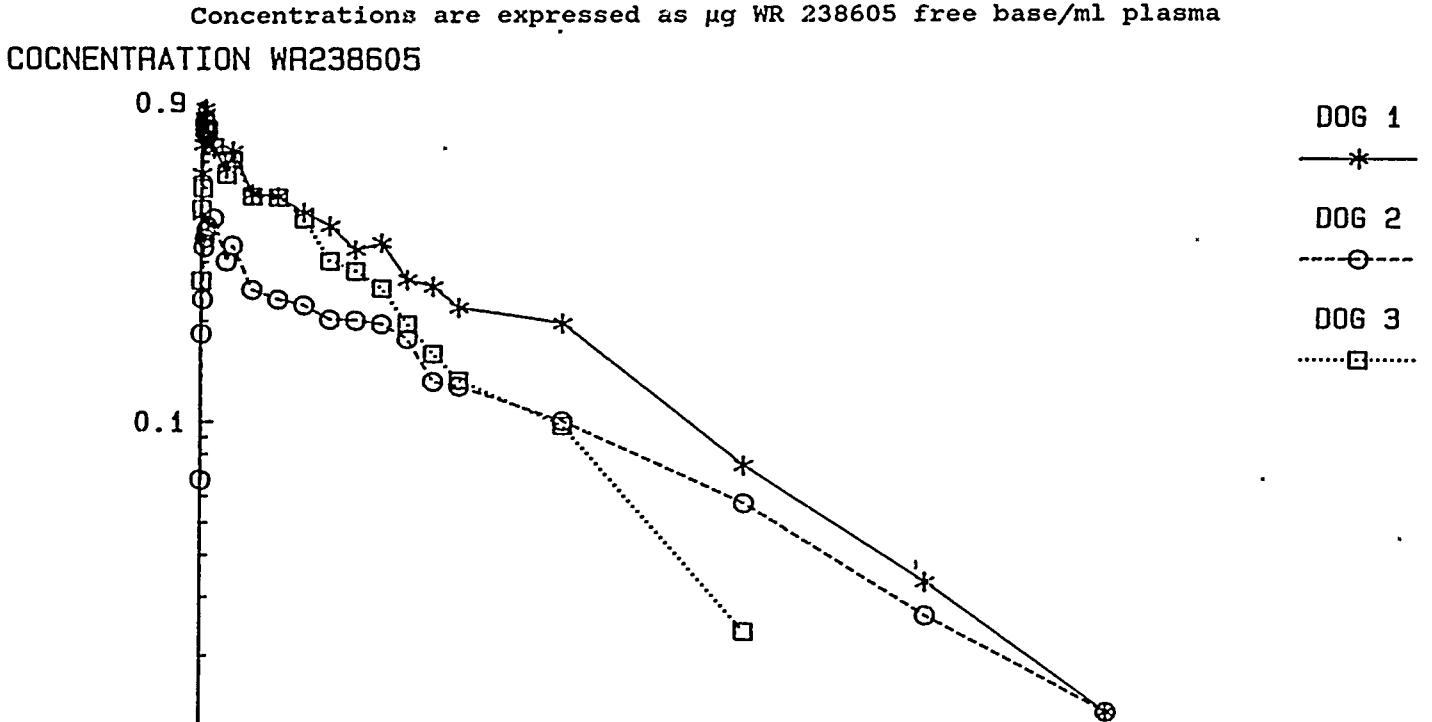


FIGURE 15

Concentrations of radioactivity in the whole-blood of beagle dogs following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml whole-blood

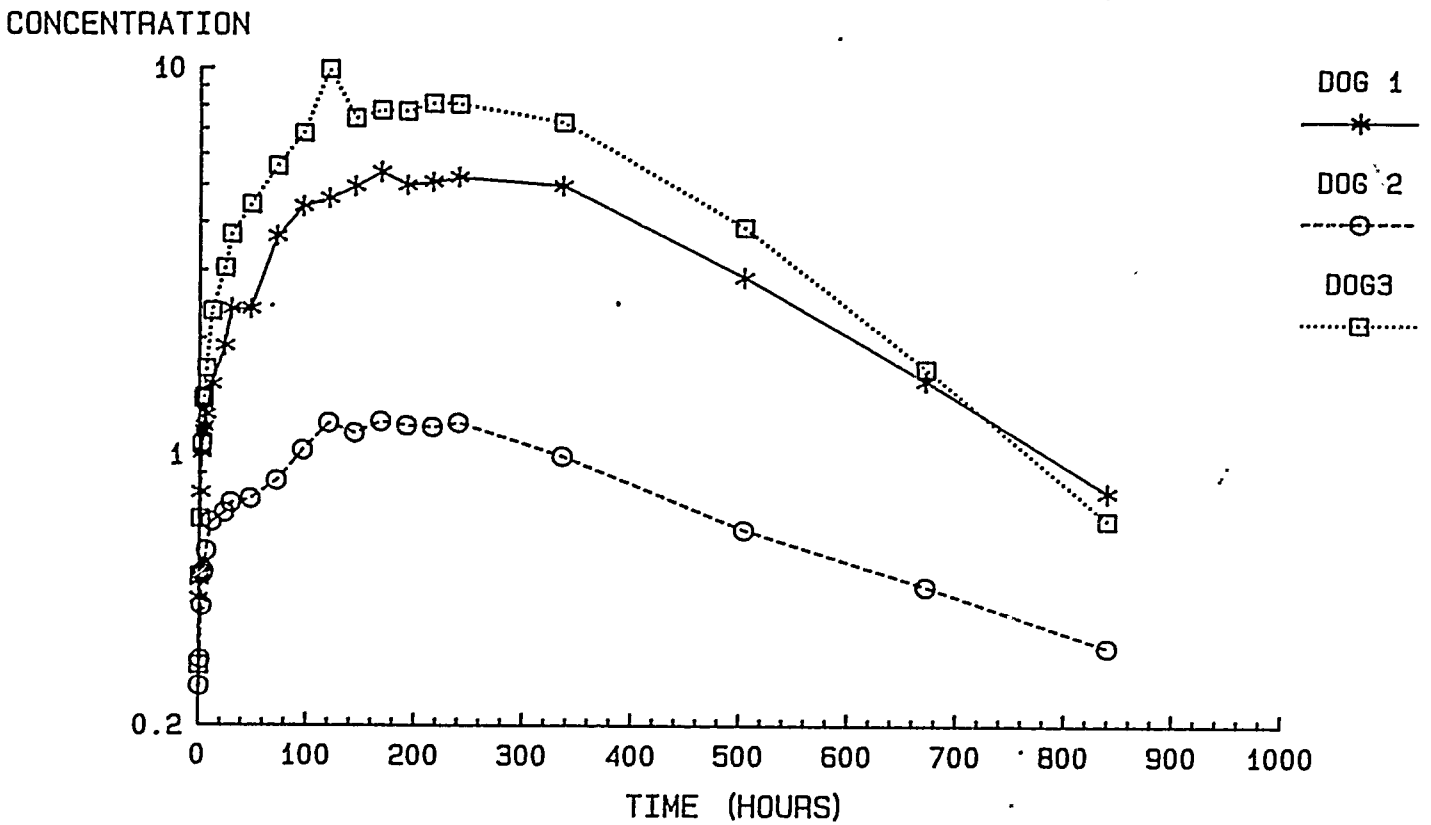


FIGURE 16

Mean concentrations of radioactivity in whole-blood and plasma and of WR 238605 in plasma of three beagle dogs following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma, or as µg equivalents of WR 238605 free base/ml whole-blood or plasma (radioactivity)

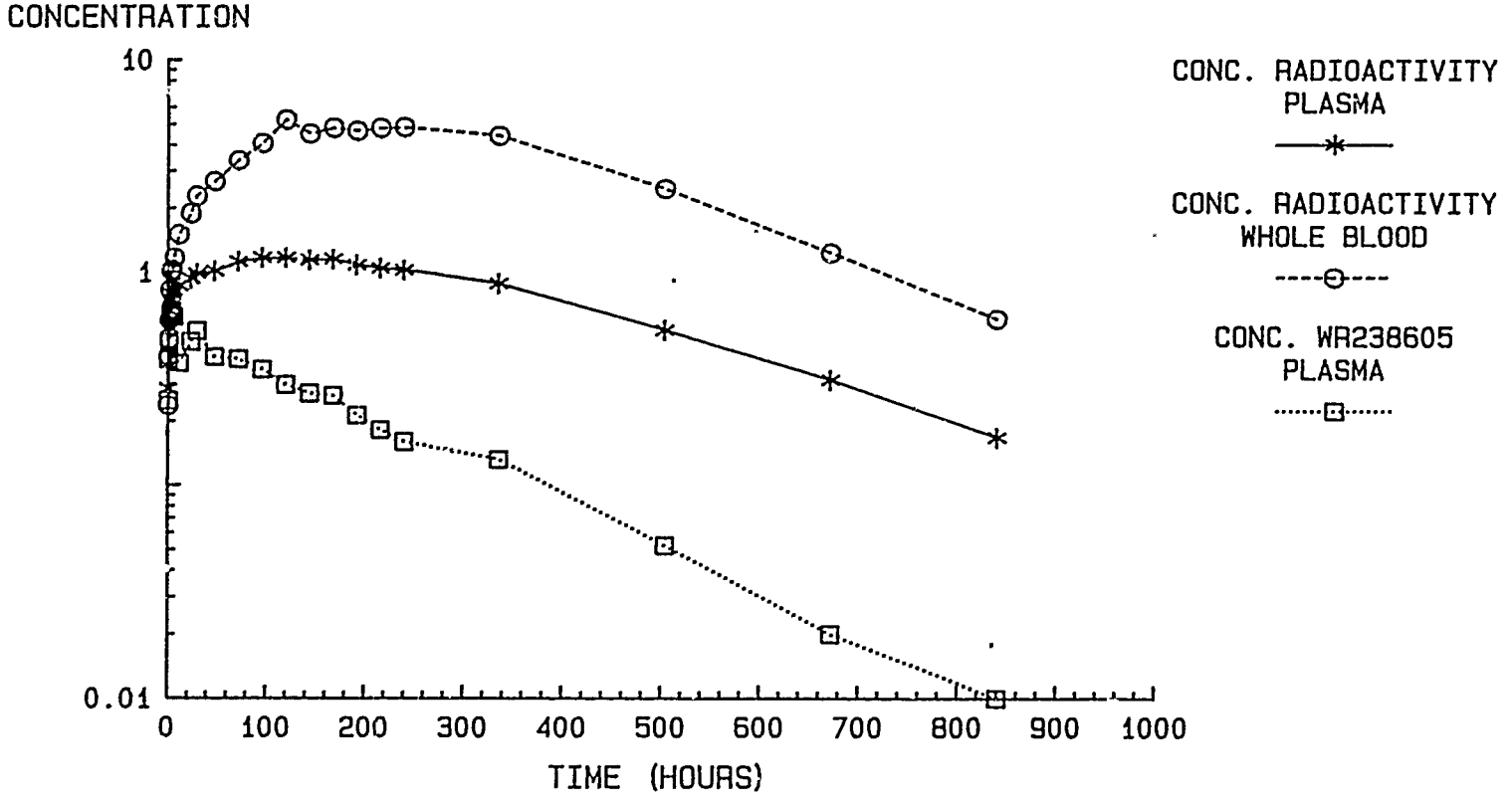


FIGURE 17

Mean concentrations of radioactivity in the plasma of three beagle dogs following oral administration of ^{14}C-WR 238605 succinate at each of four dose levels

Concentrations are expressed as µg equivalents WR 238605 free base/ml plasma

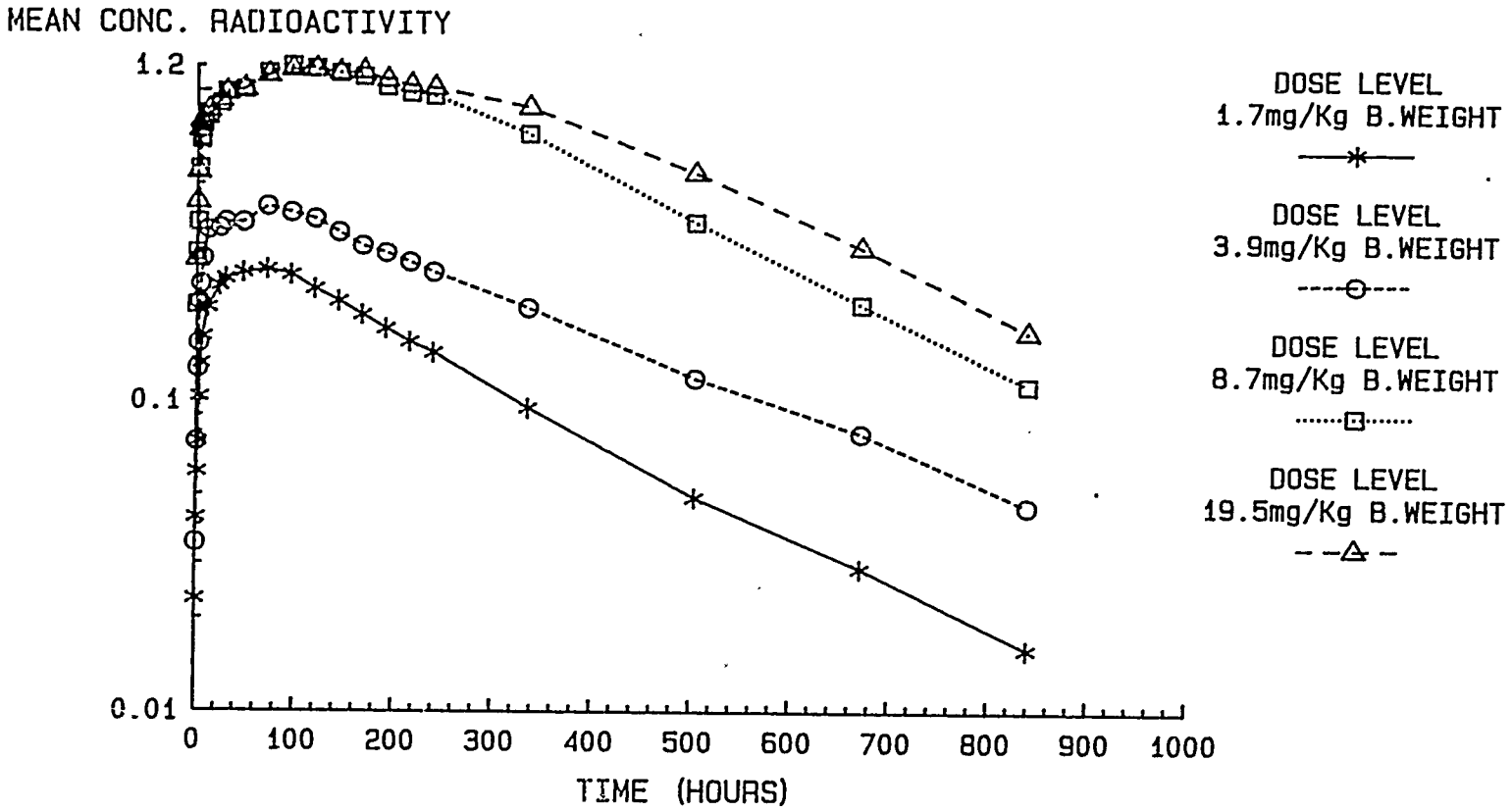


FIGURE 18a

Mean concentrations of WR 238605 in the plasma of three beagle dogs during 0.5-840 hours following oral administration of ^{14}C-WR 238605 succinate at each of four dose levels

Concentrations are expressed as µg WR 238605 free base/ml plasma

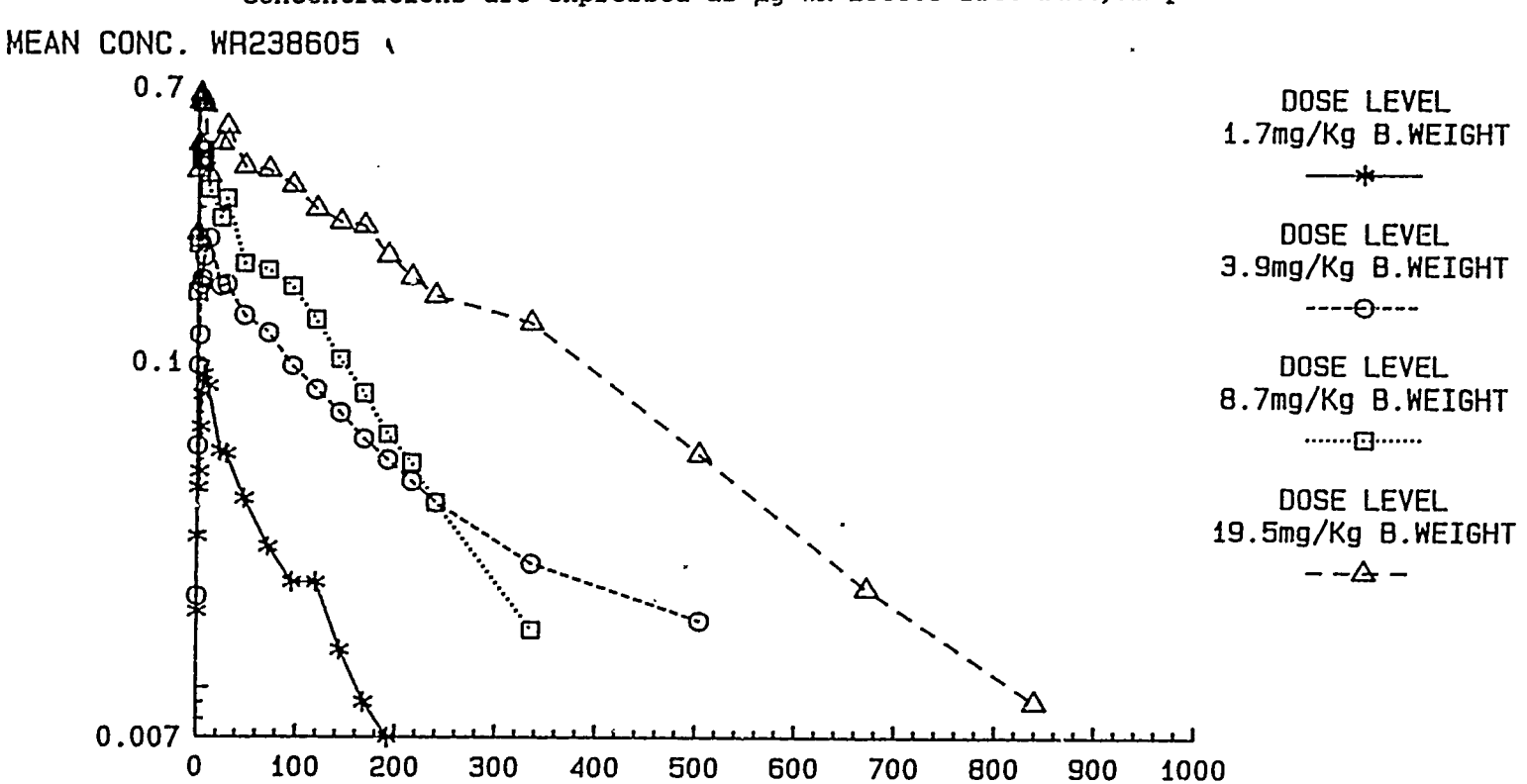


FIGURE 18b

Mean concentrations of WR 238605 in the plasma of dogs during 0-120 hours following oral administration of ^{14}C-WR 238605 succinate at four dose levels

Concentrations are expressed as µg WR 238605 free base/ml plasma

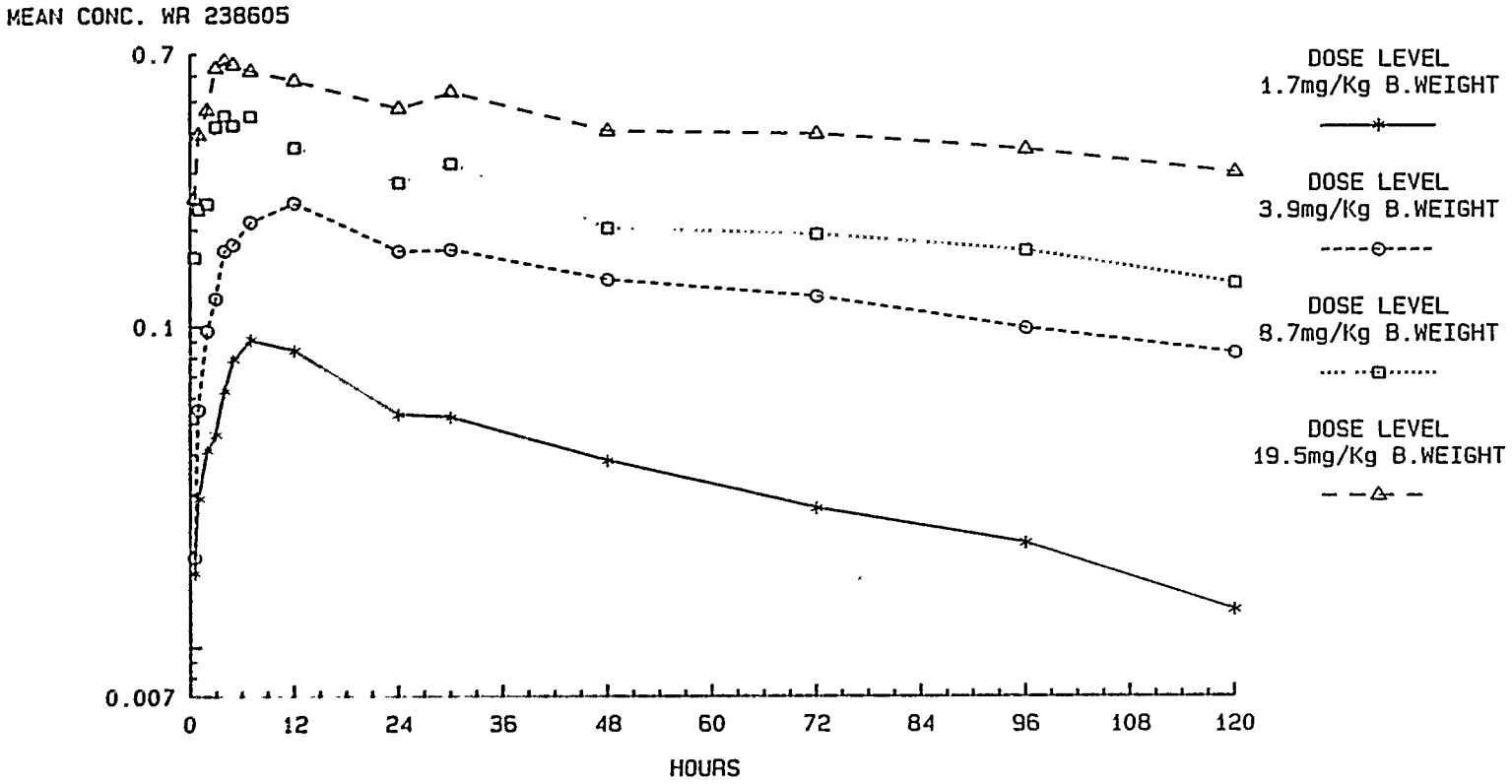


FIGURE 19

Mean concentrations of radioactivity in the whole-blood of three beagle dogs following oral administration of ^{14}C-WR 238605 succinate at each of four dose levels

Concentrations are expressed as µg equivalents WR 238605 free base/ml blood

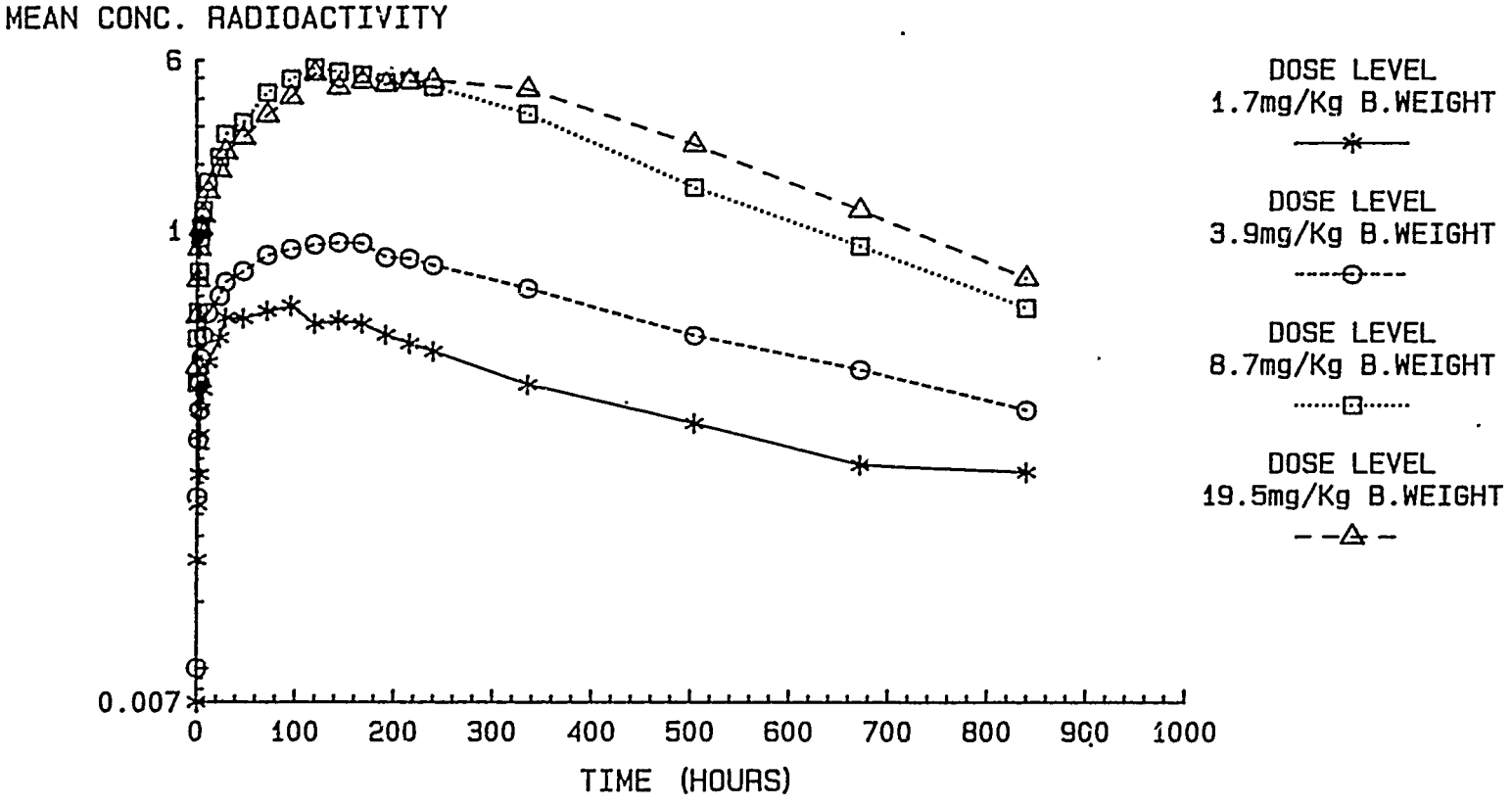


FIGURE 20

Concentrations of radioactivity in the plasma of beagle dogs following the administration of single intravenous doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml plasma

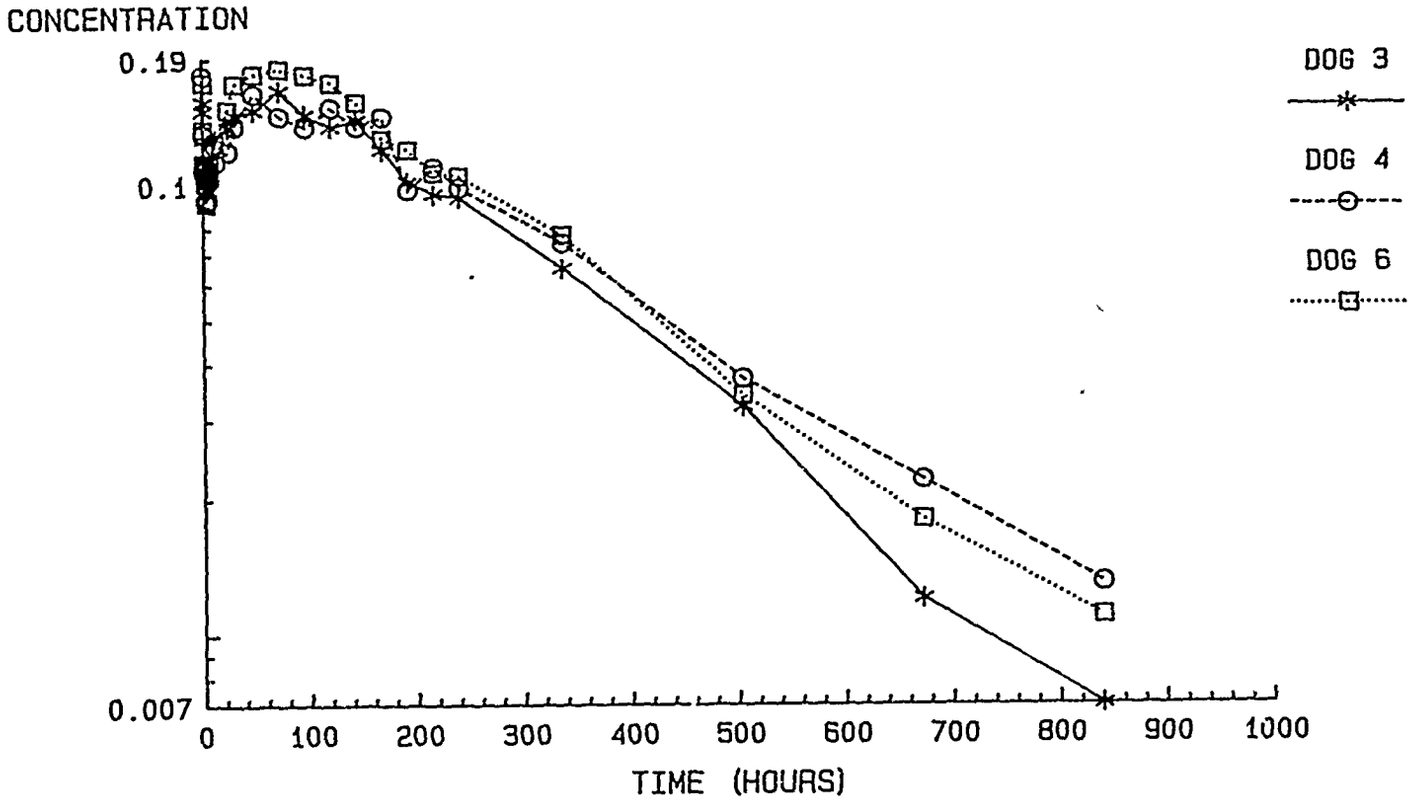


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FIGURE 21

Concentrations of WR 238605 in the plasma of beagle dogs following the administration of single intravenous doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma

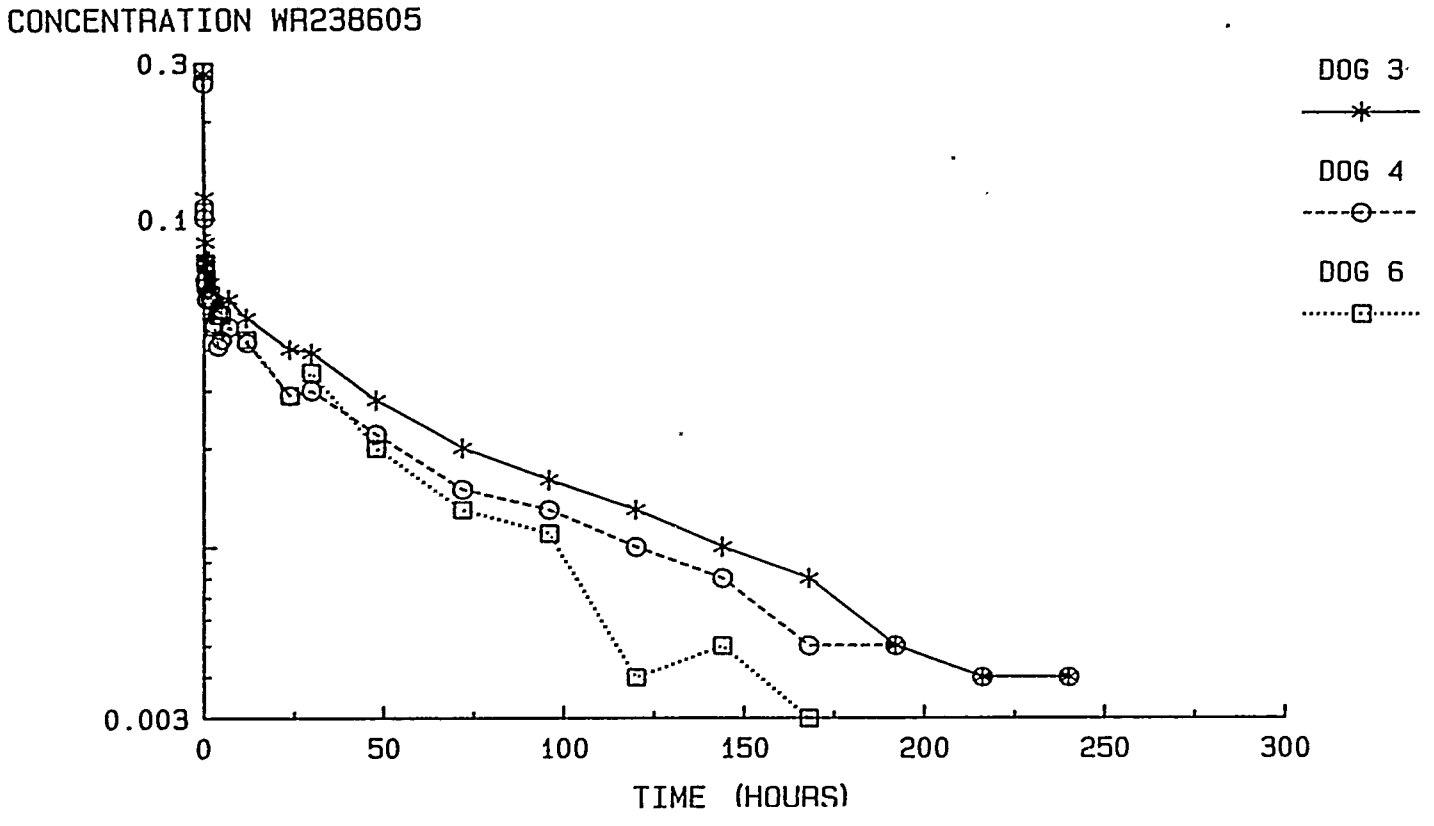


FIGURE 22

Concentrations of radioactivity in the whole-blood of beagle dogs following the administration of single intravenous doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml whole-blood

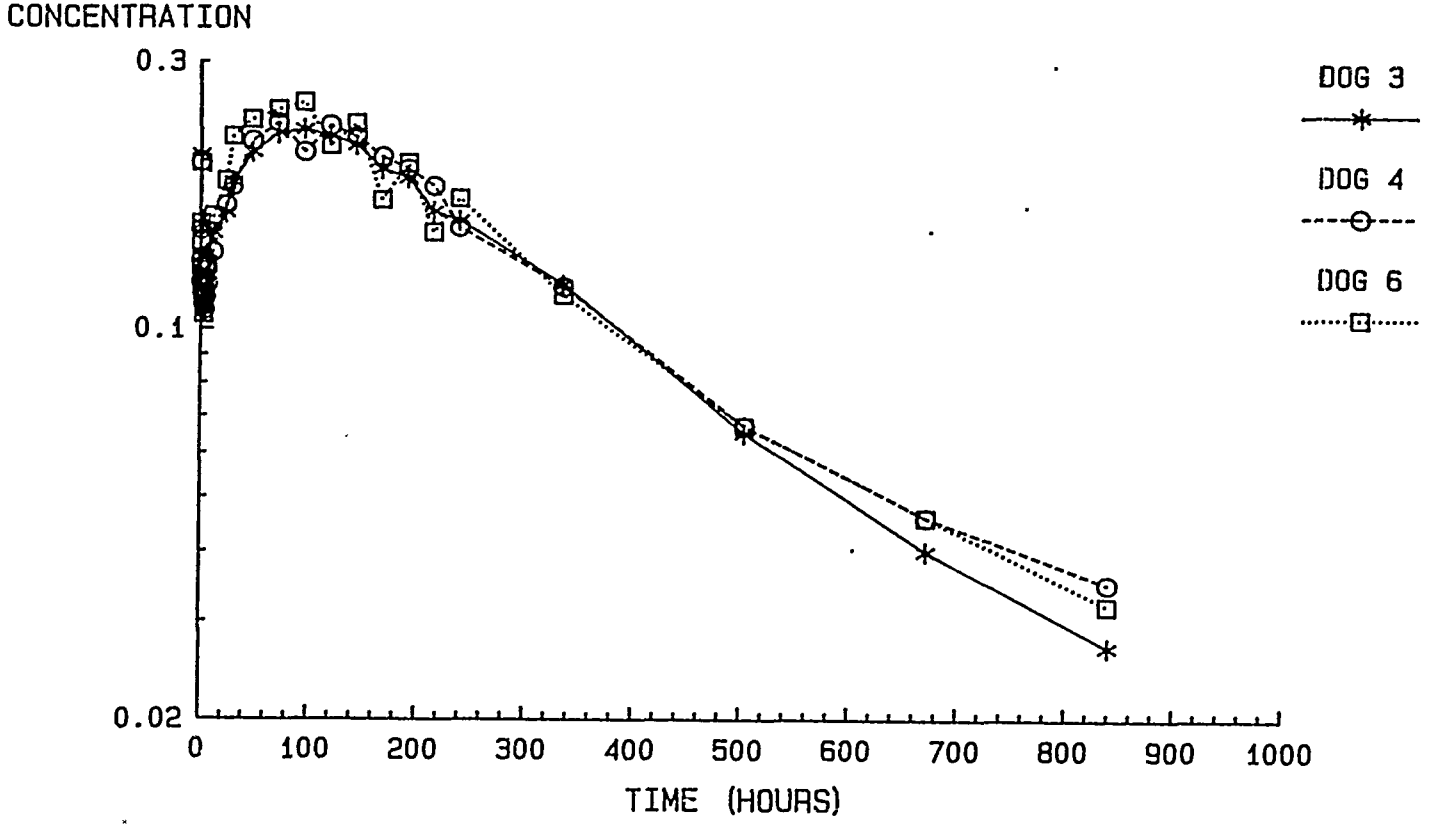


FIGURE 23

Mean concentrations of radioactivity in whole-blood and plasma and of WR 238605 in plasma of three beagle dogs following the administration of single intravenous doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma, or as µg equivalents WR 238605 free base/ml whole-blood or plasma (radioactivity)

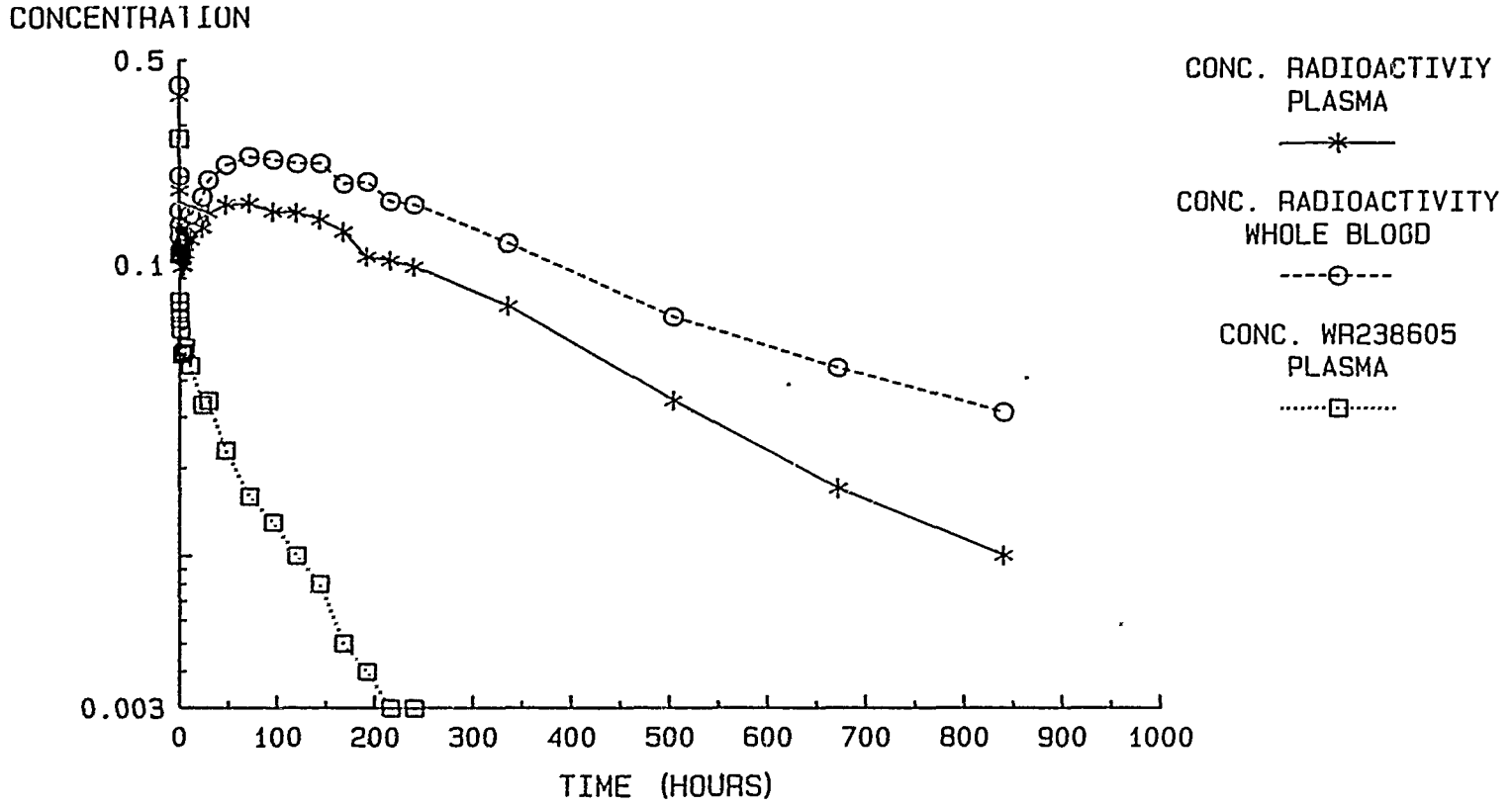


FIGURE 24

Concentrations of radioactivity in the plasma of rhesus monkeys following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml plasma

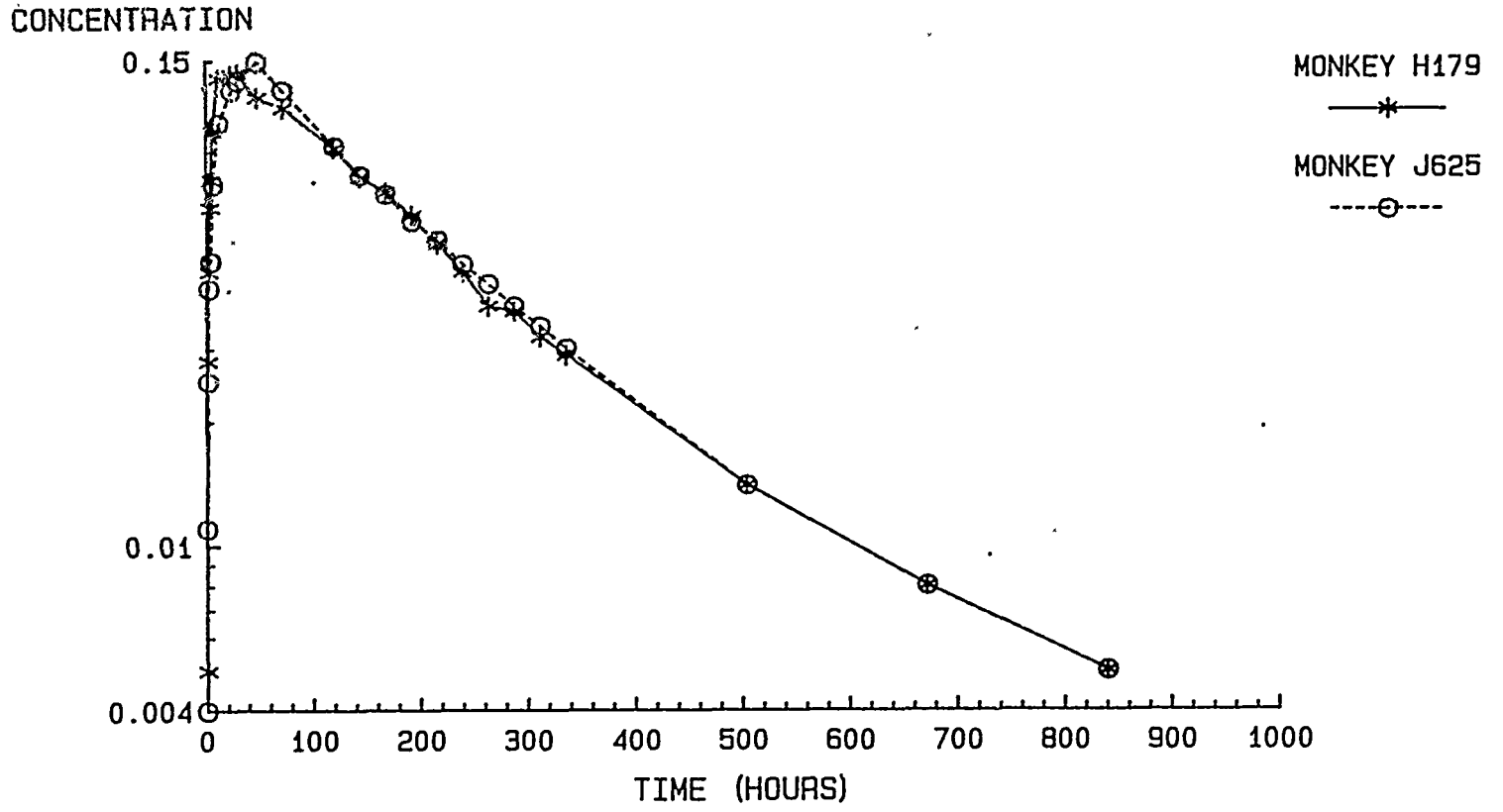


FIGURE 25

Concentrations of WR 238605 in the plasma of rhesus monkeys following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma

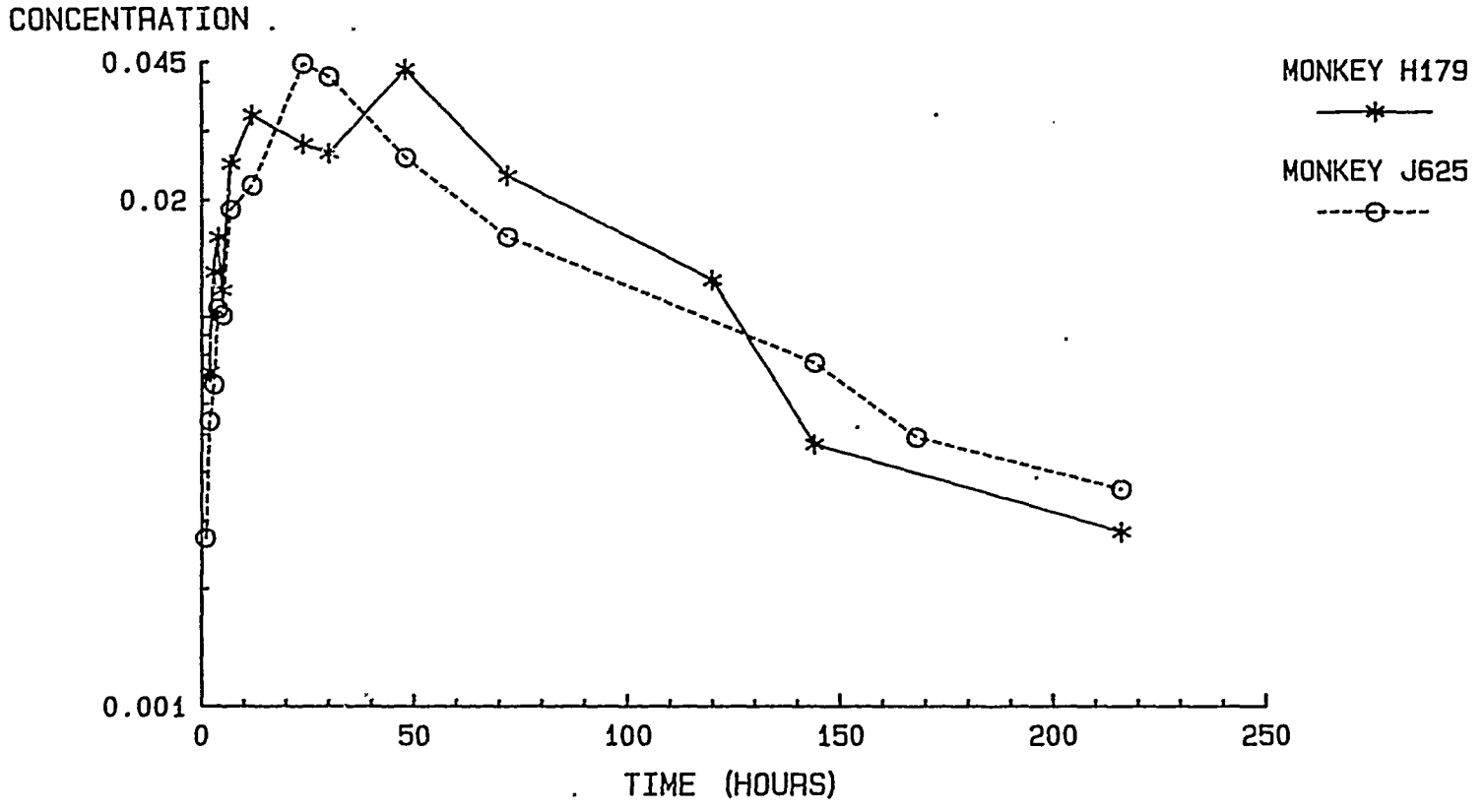
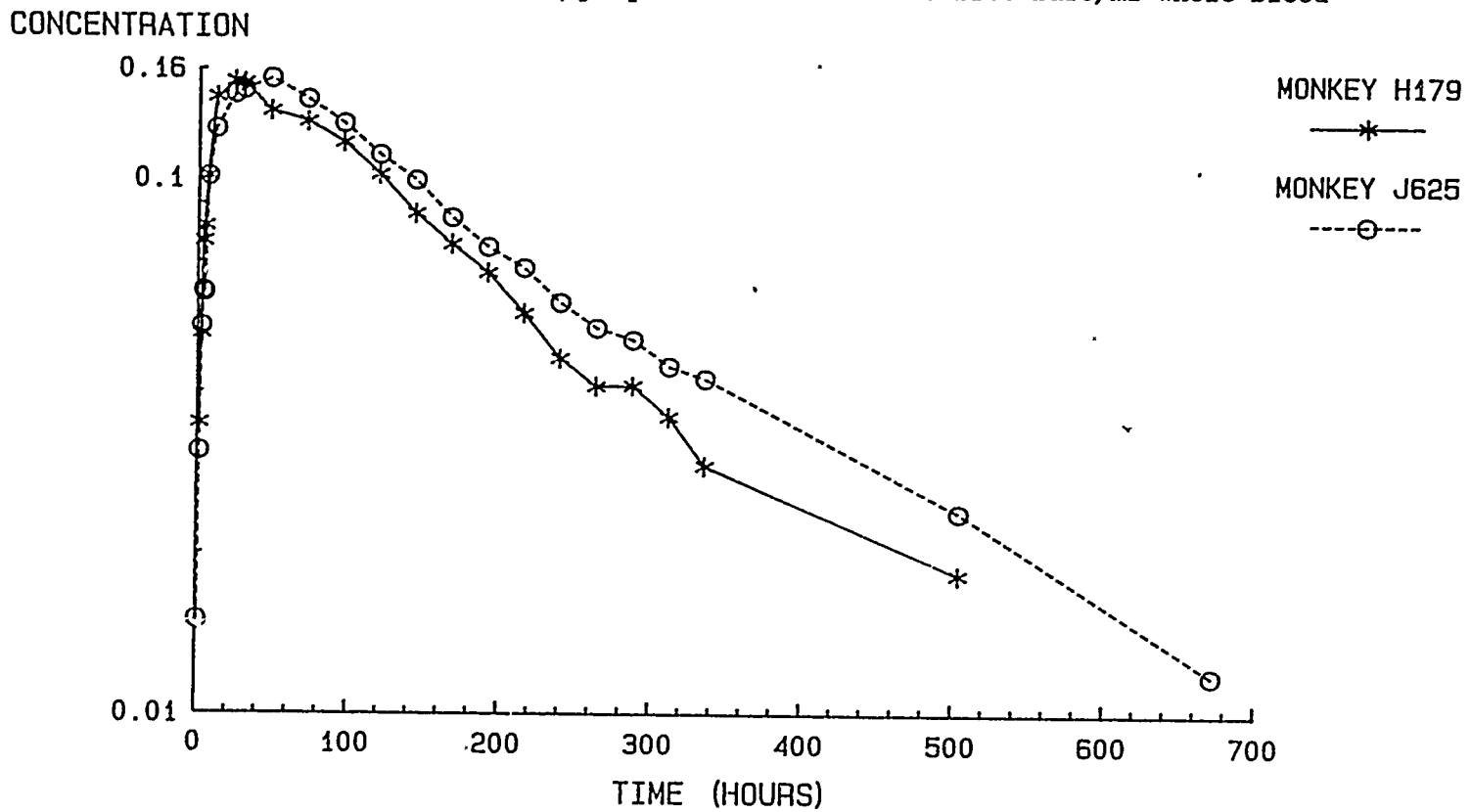


FIGURE 26

Concentrations of radioactivity in the whole-blood of rhesus monkeys following the administration of a single oral dose of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg equivalents WR 238605 free base/ml whole-blood



HRC/WRI 5/8771

FIGURE 27

Mean concentrations of radioactivity in whole-blood and plasma and of WR 238605 in plasma of two rhesus monkeys following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

Concentrations are expressed as µg WR 238605 free base/ml plasma, or as µg equivalents of WR 238605 free base/ml whole-blood or plasma (radioactivity)

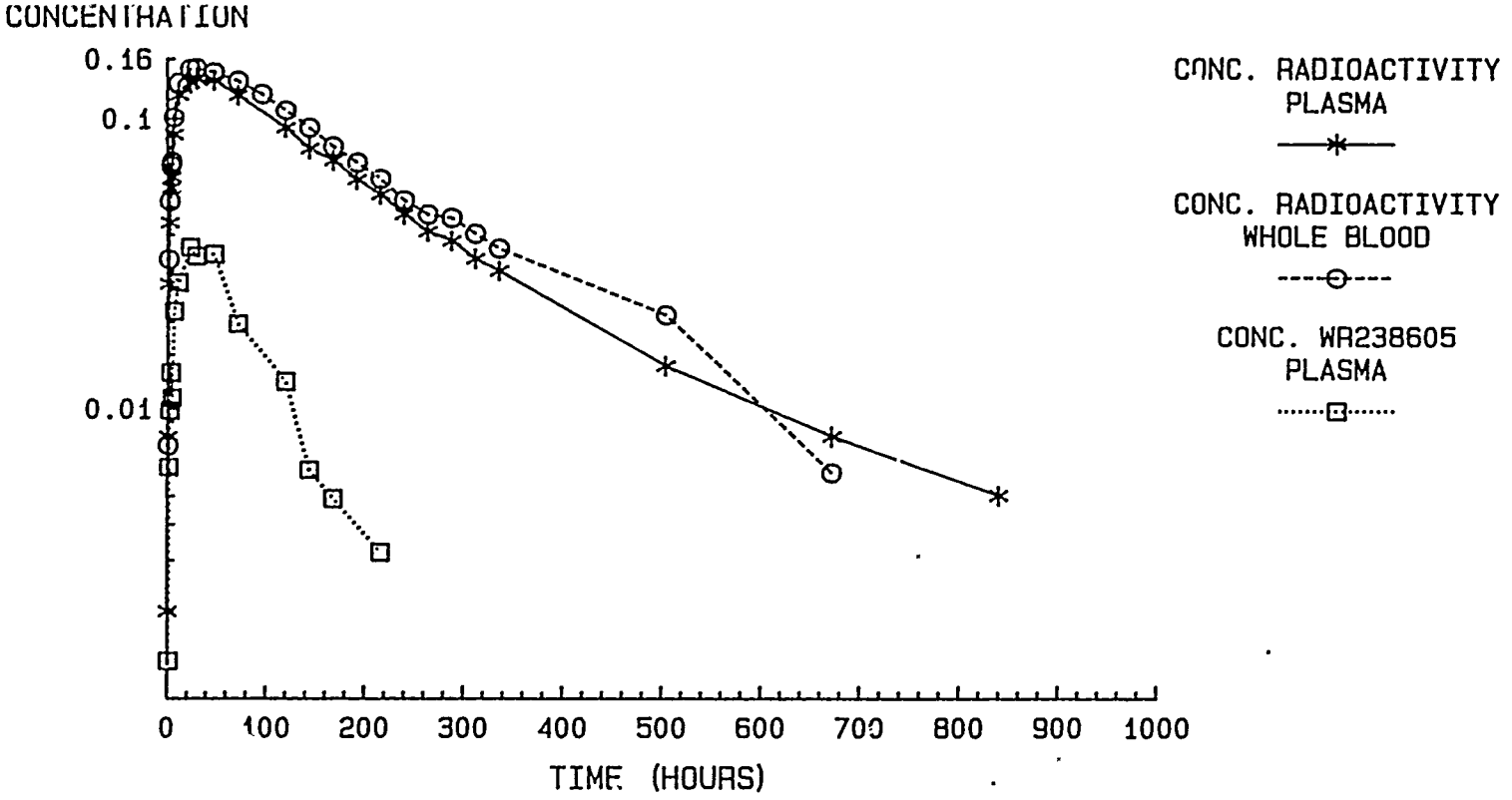


FIGURE 28

Mean cumulative excretion of radioactivity in the urine and faeces of three beagle dogs following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 1.7 mg WR 238605 free base/kg bodyweight

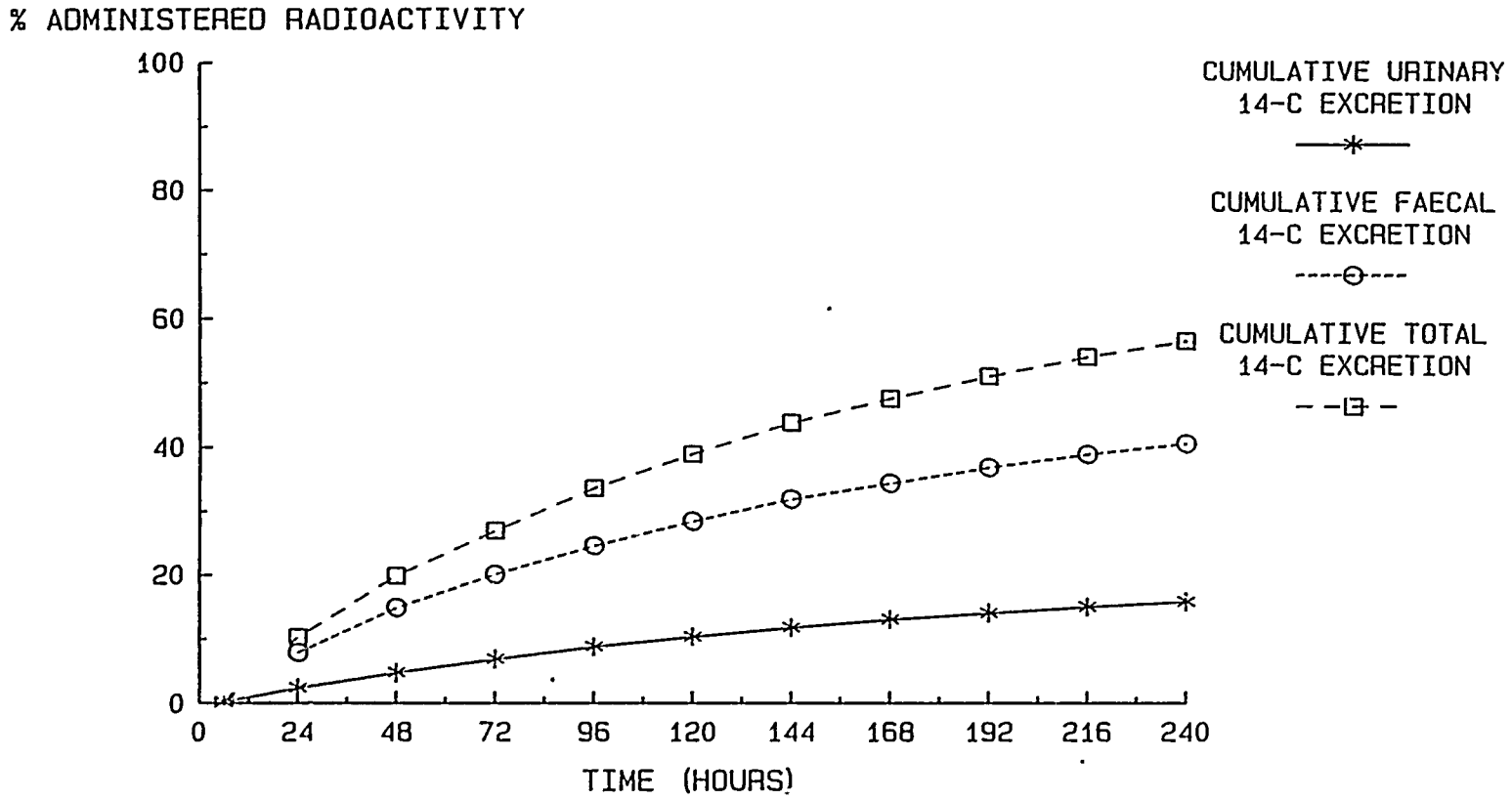


FIGURE 29

Mean cumulative excretion of radioactivity in the urine and faeces of three beagle dogs following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 3.9 mg WR 238605 free base/kg bodyweight

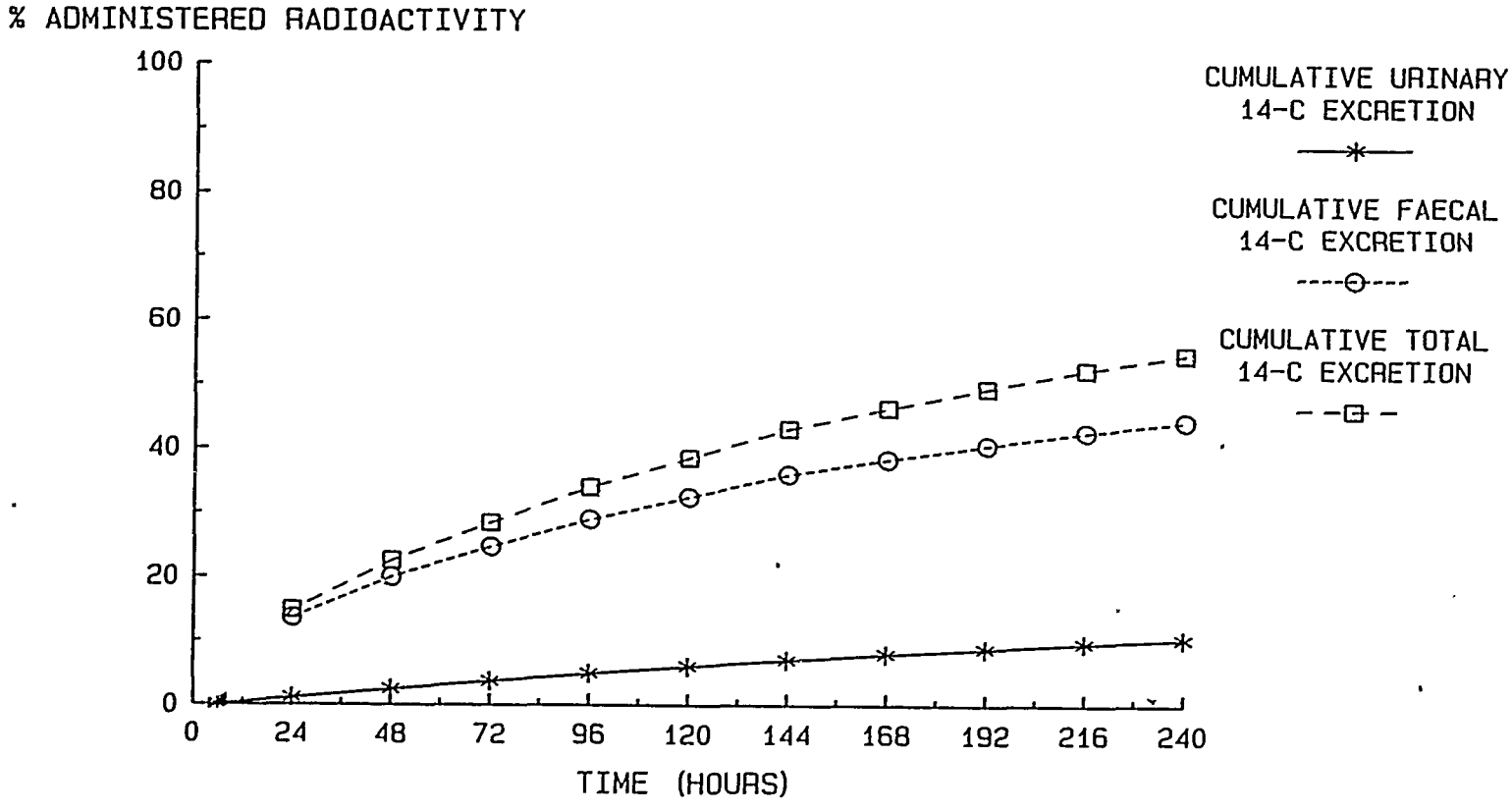


FIGURE 30

Mean cumulative excretion of radioactivity in the urine and faeces of three beagle dogs following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 8.7 mg WR 238605 free base/kg bodyweight

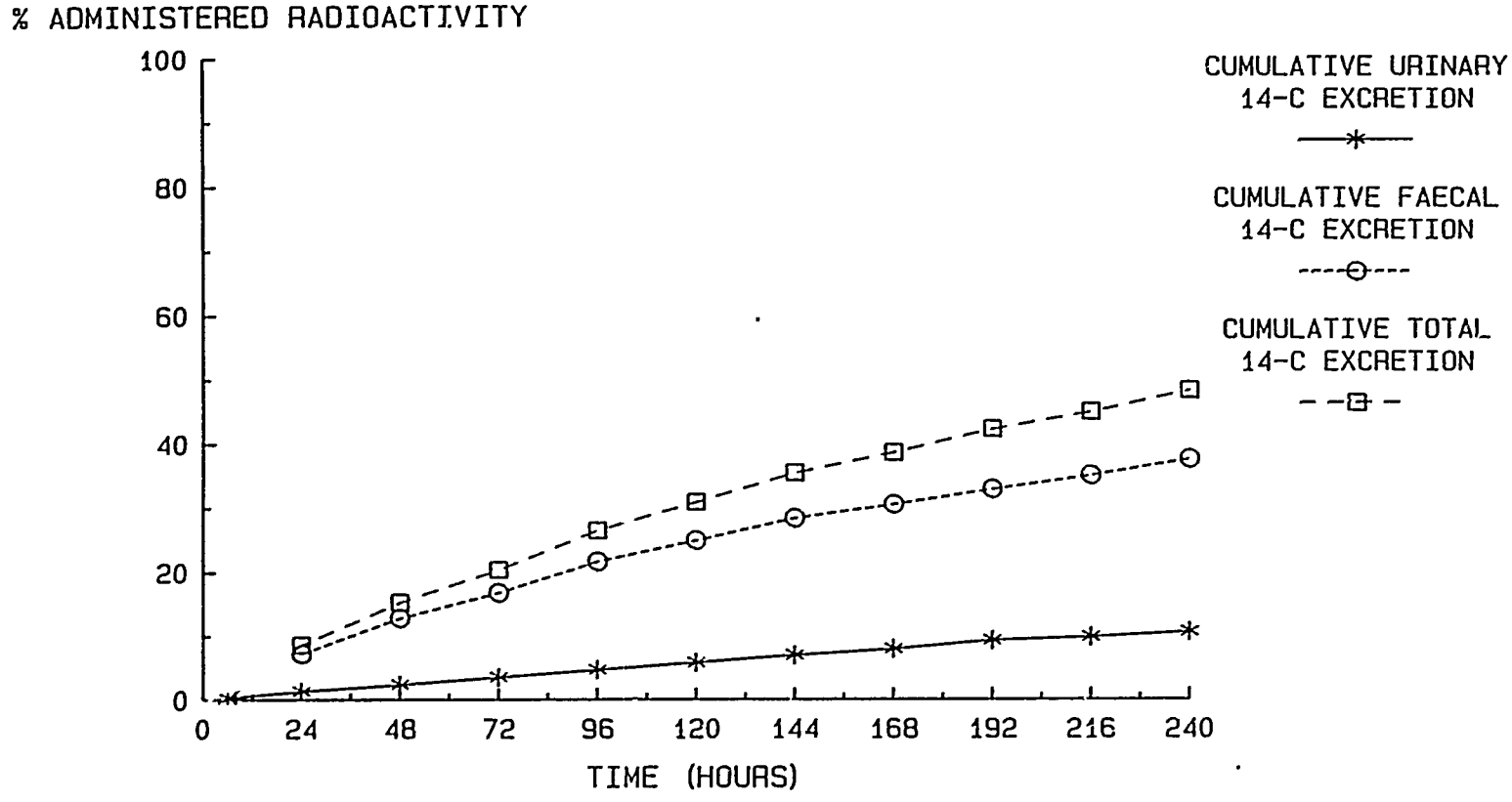


FIGURE 31

Mean cumulative excretion of radioactivity in the urine and faeces of three beagle dogs following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 19.5 mg WR 238605 free base/kg bodyweight

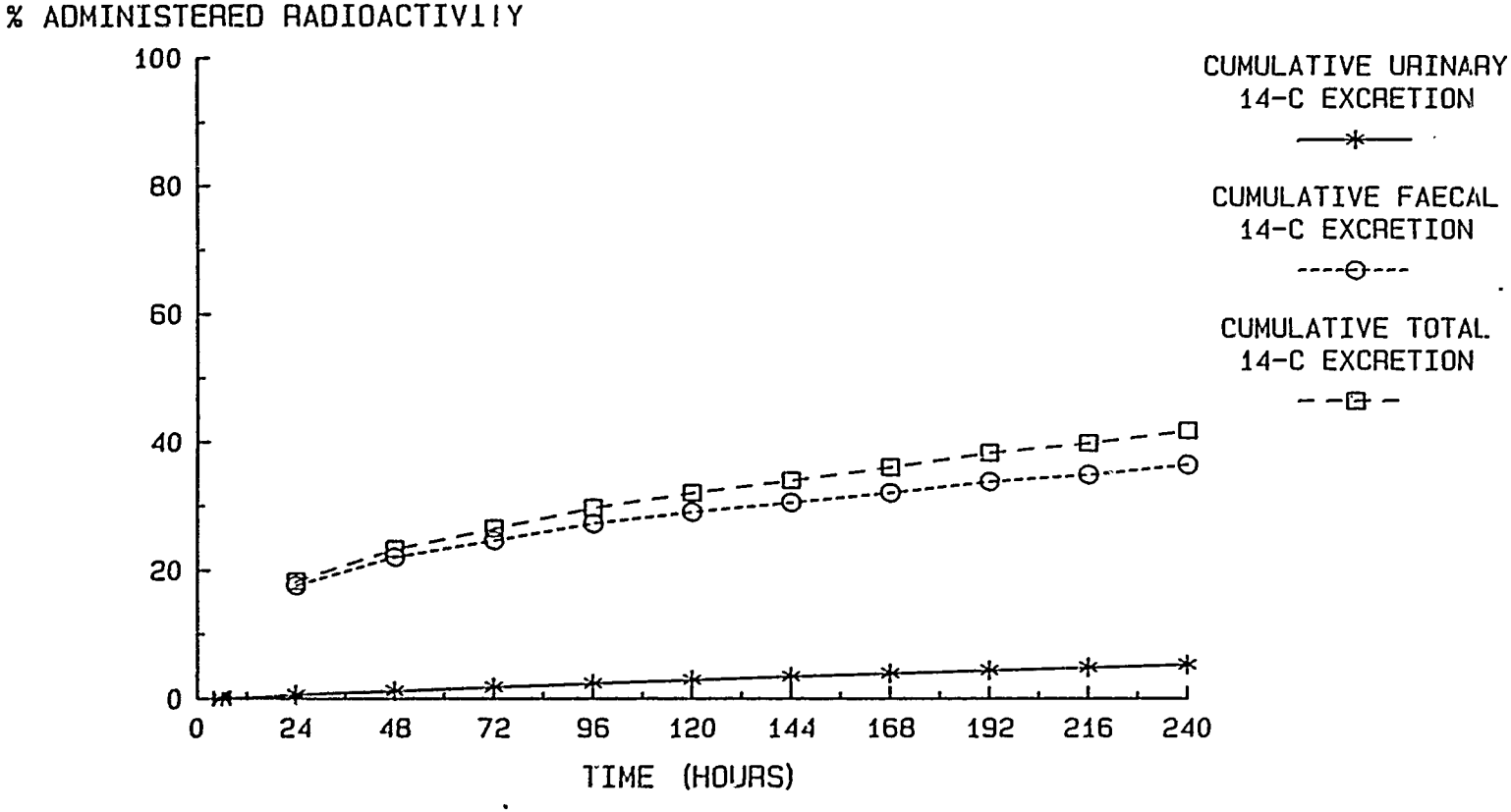


FIGURE 32

Mean cumulative excretion of radioactivity in the urine and faeces of three beagle dogs following the administration of single intravenous doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

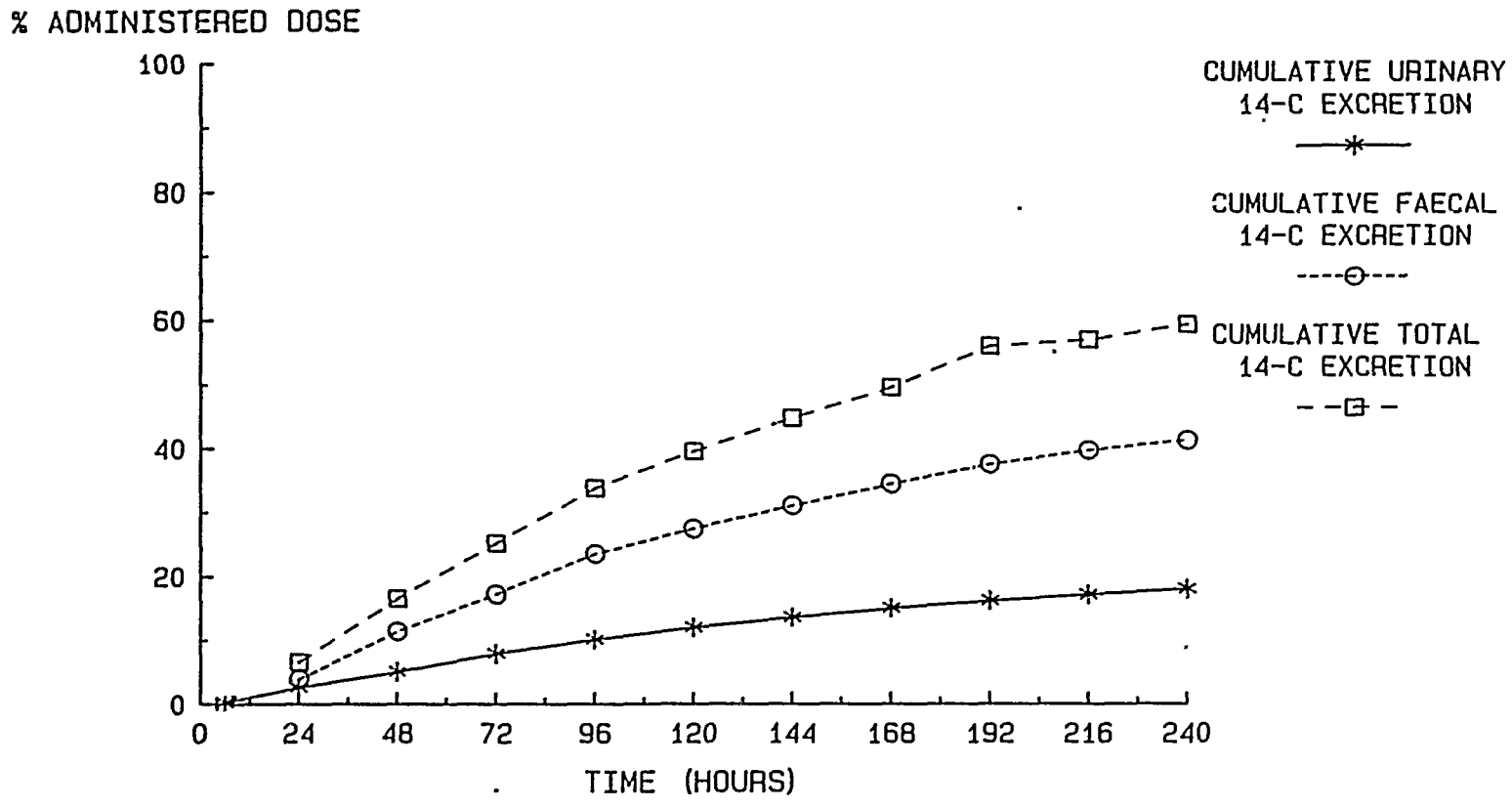


FIGURE 33

Mean cumulative excretion of radioactivity in the urine and faeces of two rhesus monkeys following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

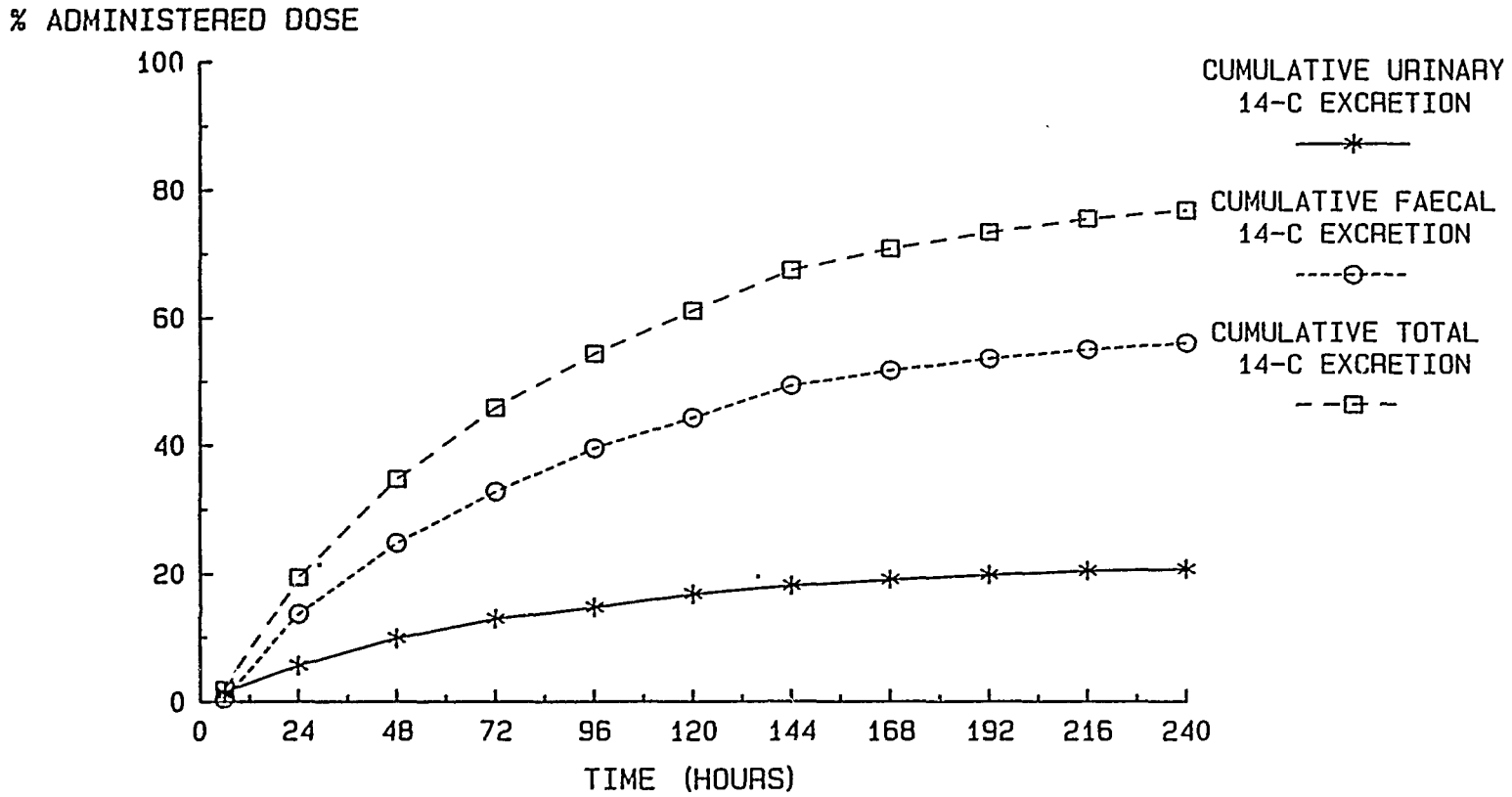


FIGURE 34

Mean rates of excretion of radioactivity in the urine following the administration of single oral doses of ^{14}C-WR 238605 succinate to beagle dogs

Dose levels shown are mg WR 238605 free base/kg bodyweight

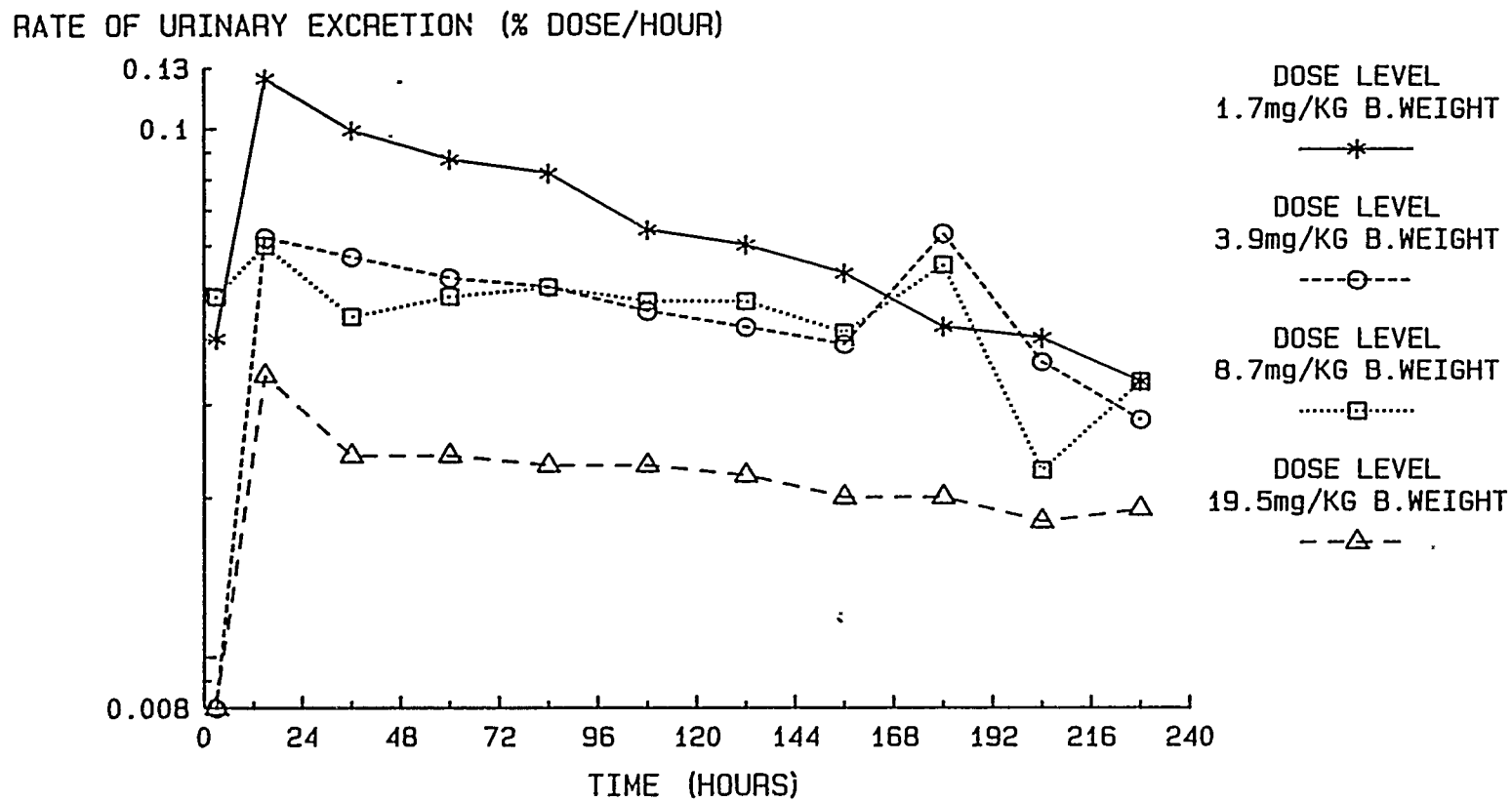


FIGURE 35

Mean rates of excretion of radioactivity in the urine of three beagle dogs following the administration of single intravenous doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

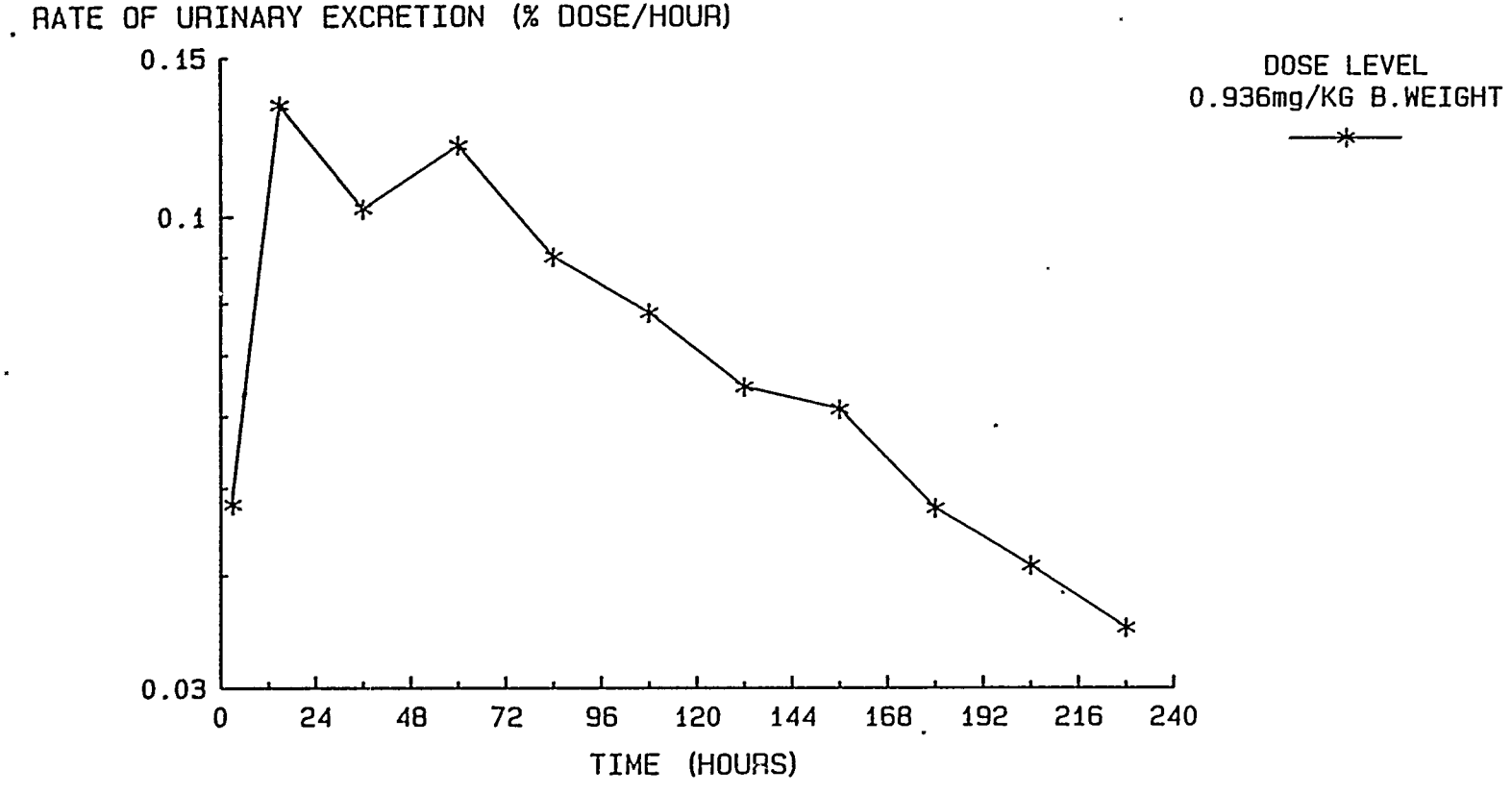


FIGURE 36

Mean rates of excretion of radioactivity in the urine of two rhesus monkeys following the administration of single oral doses of ^{14}C-WR 238605 succinate at a dose level of 0.936 mg WR 238605 free base/kg bodyweight

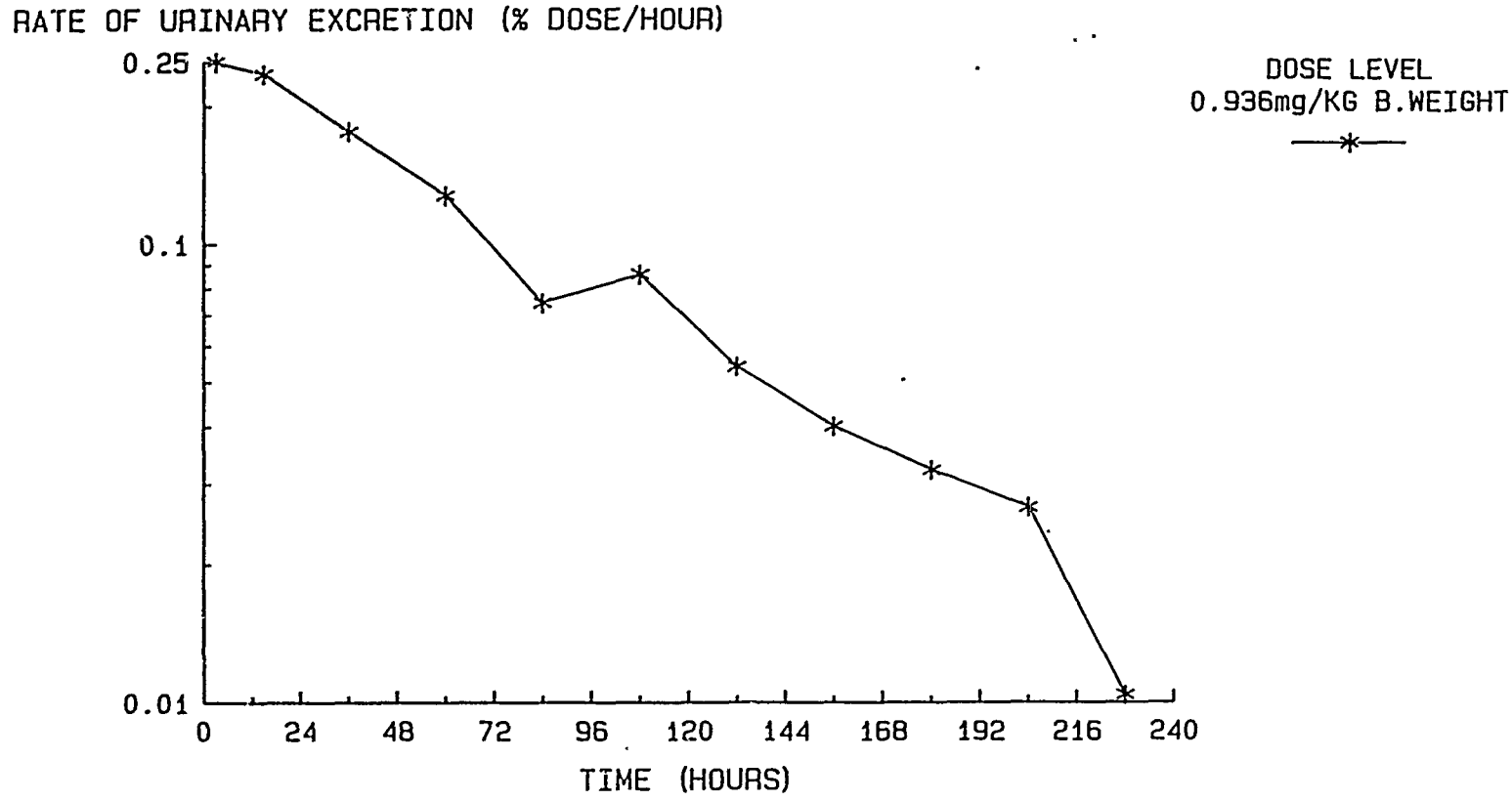


FIGURE 37

Representative radiochromatogram scans of thin-layer separations of extracts of urine collected following the administration of ^{14}C-WR 238605 succinate to beagle dogs and rhesus monkeys

Kieselgel 60 F_{254} plates developed in methanol : 35% aqueous ammonia, 25 : 1 (v/v)

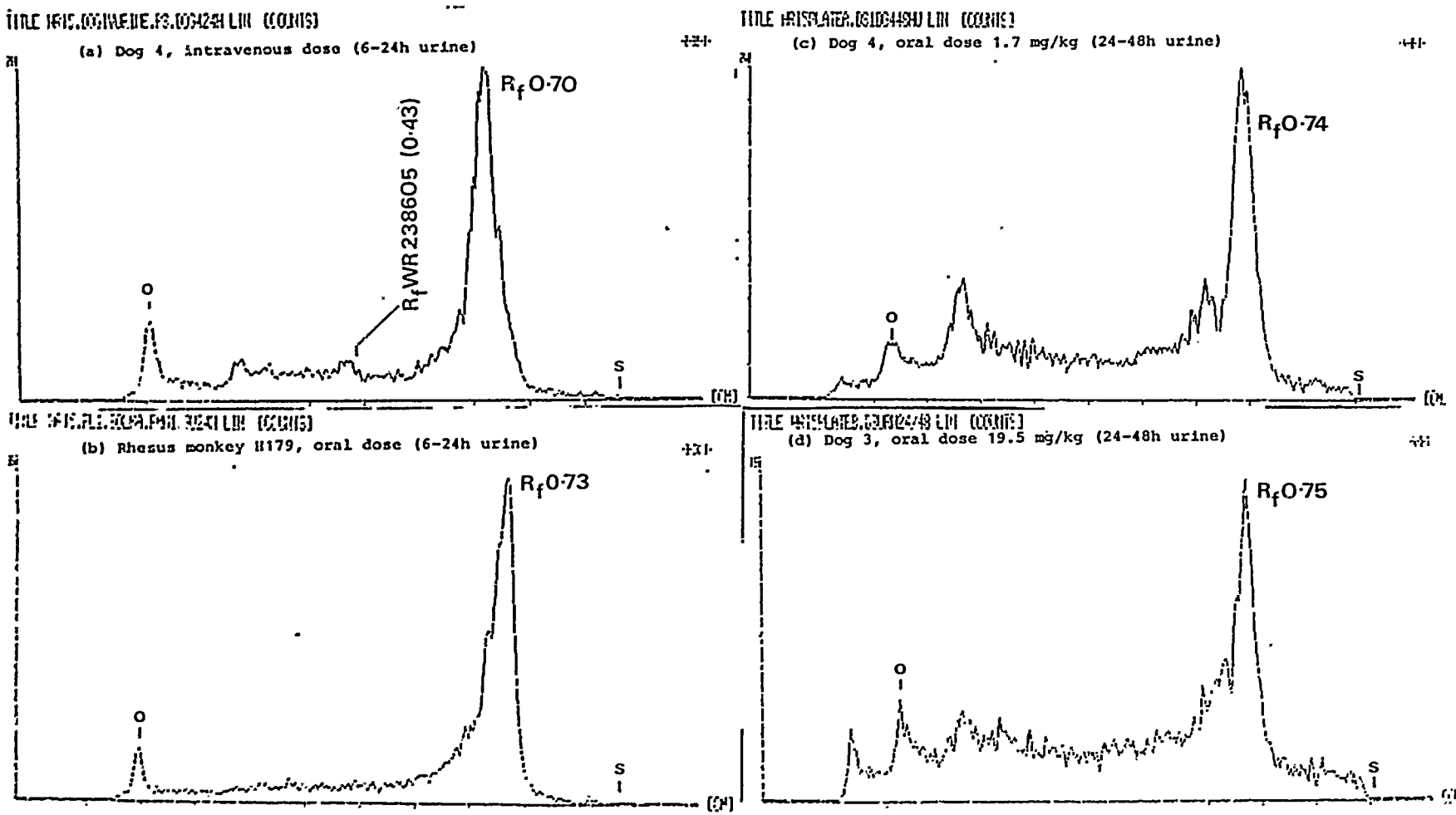


FIGURE 38

Radiochromatogram scans of thin-layer separations of methanol extracts of faeces collected following the administration of ^{14}C-WR 238605 succinate to beagle dogs and rhesus monkeys
Kieselgel 60 F_{254} plates developed in methanol : 35% aqueous ammonia, 25 : 1 (v/v)

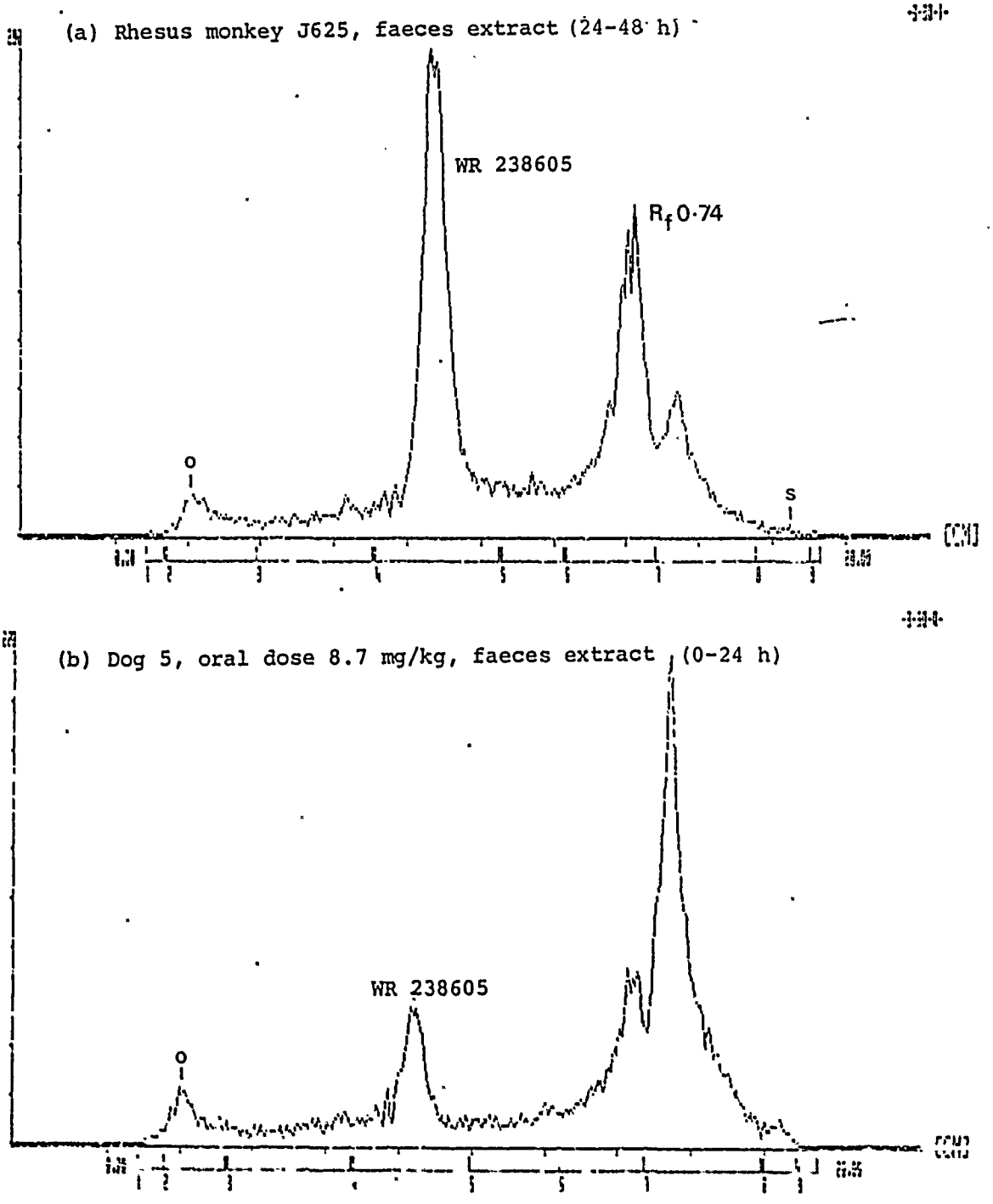


FIGURE 39

Radiochromatogram scans of thin-layer separations of extracts of plasma samples collected following the administration of ^{14}C-WR 238605 succinate to beagle dogs
Kieselgel 60 F_{254} plates developed in methanol : 35% aqueous ammonia, 25 : 1 (v/v)

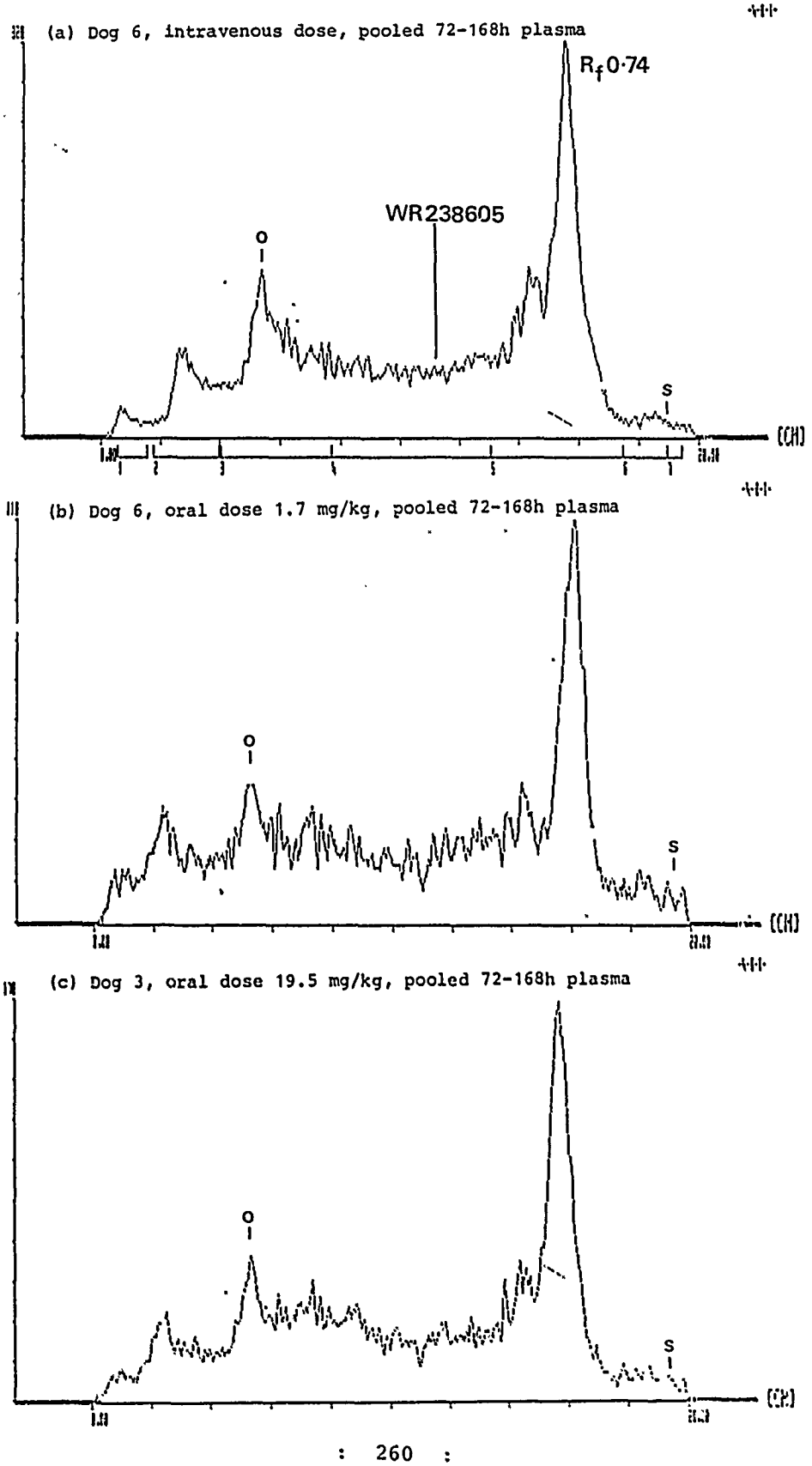
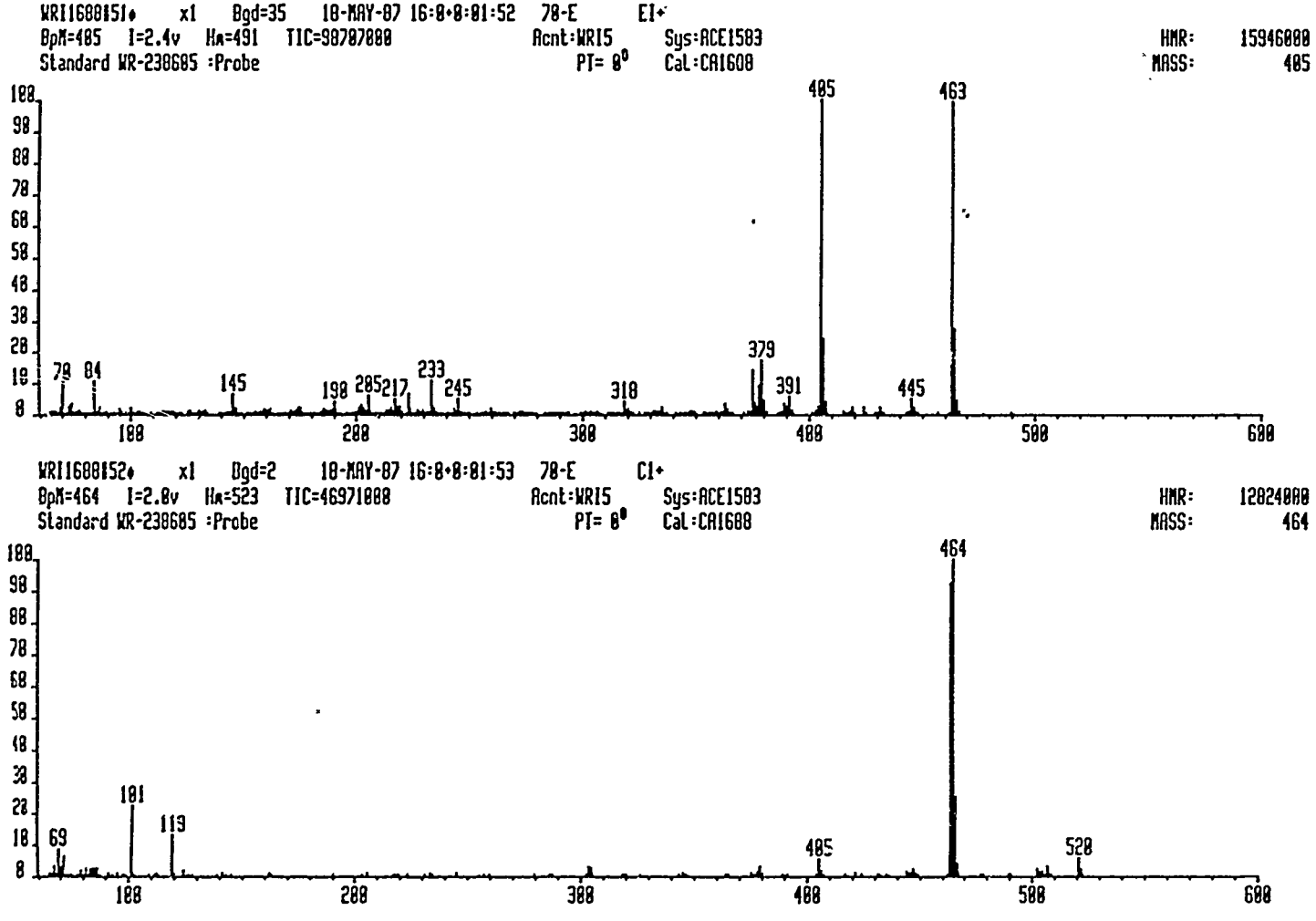


FIGURE 40

Electron Impact (upper) and Chemical Ionisation (lower) mass spectra
for WR 238605



PLASMA CONCENTRATIONS AND RELATIVE BIOAVAILABILITY OF THREE PYRIDOSTIGMINE SUSTAINED RELEASE FORMULATIONS AFTER SINGLE ORAL DOSES TO DOGS

SUMMARY

1. Plasma concentrations of pyridostigmine base and relative drug bioavailability have been measured after single oral doses of 10 mg of the bromide salt as three sustained release tablet formulations of differing in vitro release rates to 6 dogs in a crossover study. One tablet (Formulation A) released 100% of its drug content during 6 hours of an in vitro dissolution test, another tablet (Formulation B) released 95.5% during 12 hours and the third tablet (Formulation C) released 74.9% during 12 hours.

2. After single oral doses of 10 mg of the bromide salt to dogs, the peaks of mean plasma concentrations of pyridostigmine base of 20.0 ± 7.5 SD ng/ml, 22.8 ± 15.6 SD ng/ml and 23.0 ± 16.8 SD ng/ml occurred at 3 hours, 3 hours and 4 hours respectively after administration of Formulations A, B and C respectively. After reaching the peak levels, mean plasma drug concentrations declined slowly to 4.7 ng/ml, 5.3 ng/ml and 5.9 ng/ml at 12 hours after administration of Formulations A,B and C respectively.

3. The means of the peak concentrations of pyridostigmine base in the plasma of individual dogs were 21.5 ng/ml ± 8.1 SD, 25.0 ng/ml ± 14.3 SD and 24.3 ng/ml ± 16.2 SD after single oral doses of 10 ng of the bromide salt in Formulations A, B and C respectively. The peak levels occurred at mean times of 3.4 hours, 3.5 hours and 3.1 hours respectively. A terminal first-order rate constant (or half-life) of plasma pyridostigmine concentration could not be calculated.

4. The mean areas under the plasma pyridostigmine base concentration to the last sampling time (AUC_{12}) were 135.3 ng.h/ml ± 65.8 SD, 143.5 ng.h/ml ± 99.1 SD and 159.8 ng.h/ml ± 111.0 SD after single oral doses of 10 mg of the bromide salt as Formulations A, B and C respectively. The AUC_{12} ratios for comparisons of interest were 1.06(B/A), 1.18(C/A) and 0.90(B/C).

5. Analyses of variance of mean peak plasma concentrations, times of their occurrence and AUC_{12} indicated that none of these parameters after the administration of any formulation was statistically significantly different ($P>0.05$). Despite the relatively large differences in drug dissolution rates from these formulations, these differences were apparently not reflected by the <u>in vivo</u> bioavailability parameters.

TABLE 1

Concentrations of pyridostigmine in the plasma of dogs after single oral doses of 10 mg of the bromide salt as Formulation A

Results are expressed as ng/ml

Time (hours)	Subject number						
	1	2	3	4	5	6	Mean
00	ND	ND	ND	ND	ND	ND	-
0.25	5.94	ND	ND	ND	ND	ND	-
0.5	6.20	ND	ND	3.50	ND	ND	-
0.75	6.67	ND	1.77	10.9	ND	1.90	3.54
1.0	8.65	2.52	3.93	13.7	3.79	2.17	5.79
1.3	12.8	3.80	4.72	19.0	6.90	2.94	8.36
1.7	18.1	14.5	4.35	19.8	13.5	5.36	12.60
2.0	19.0	17.5	10.6	21.1	12.0	5.51	14.28
2.5	21.4	21.6	16.0	21.2	20.6	6.82	17.94
3.0	26.7	23.6	17.2	26.2	19.3	6.80	19.97
3.5	28.7	22.4	11.0	25.4	17.1	6.96	18.59
4.0	28.7	20.4	10.7	24.4	26.0	6.84	19.51
5.0	20.7	19.4	7.68	24.5	21.9	3.84	16.34
6.0	14.5	17.9	6.82	25.7	20.2	2.38	14.58
7.0	14.4	16.3	7.32	18.7	21.2	2.62	13.42
8.0	11.7	12.2	4.03	17.2	16.4	2.20	10.62
10.0	10.8	4.85	ND	9.70	5.78	2.89	5.67
12.0	7.37	4.38	ND	8.52	4.91	2.76	4.66

ND Not detected (<1.50 ng/ml)

TABLE 2

Plasma concentrations of pyridostigmine (Treatment A)
statistical analysis of data on Table 1

Time (hours)	Mean (ng/ml)	Maximum (ng/ml)	Minimum (ng/ml)	Standard deviation (ng/ml)	Coefficient of variation (%)
00	ND	ND	ND	-	-
0.25	ND	5.94	ND	-	-
0.5	1.62	6.20	ND	2.65	164
0.75	3.54	10.9	ND	4.36	123
1.0	5.79	13.7	2.17	4.52	78
1.3	8.36	19.0	2.94	6.30	75
1.7	12.60	19.8	4.35	6.43	51
2.0	14.28	21.1	5.51	5.91	41
2.5	17.94	21.6	6.82	5.84	33
3.0	19.97	26.7	6.80	7.47	37
3.5	18.59	28.7	6.96	8.46	46
4.0	19.51	28.7	6.84	8.83	45
5.0	16.34	24.5	3.84	8.45	52
6.0	14.58	25.7	2.38	8.66	59
7.0	13.42	21.2	2.62	7.09	53
8.0	10.62	17.2	2.20	6.24	59
10.0	5.67	10.8	ND	4.08	72
12.0	4.66	8.52	ND	3.09	66

ND Not detected (<1.50 ng/ml)

TABLE 3

Concentrations of pyridostigmine base in plasma of dogs after single oral doses of 10 mg of the bromide salt as Formulation B

Results are expressed as ng/ml

Time (hours)	Subject number						
	1	2	3	4	5	6	Mean
00	ND	ND	ND	ND	ND	ND	-
0.25	ND	ND	3.68	ND	3.20	ND	-
0.5	ND	ND	4.02	4.63	4.12	ND	2.13
0.75	2.97	2.41	9.62	3.03	6.47	7.03	5.25
1.0	4.84	4.26	12.2	3.08	8.56	7.91	6.81
1.3	5.73	7.37	28.7	6.27	14.5	12.3	12.48
1.7	7.34	6.95	35.8	7.69	19.8	13.3	15.15
2.0	3.11	8.62	43.4	8.69	22.0	17.6	17.24
2.5	12.2	9.91	44.2	7.79	26.1	18.5	19.78
3.0	14.5	14.1	51.4	8.56	28.9	19.1	22.76
3.5	17.9	16.3	48.5	9.09	22.7	21.2	22.61
4.0	21.9	14.5	41.7	10.3	20.6	17.1	21.02
5.0	18.3	13.1	39.5	7.55	13.7	12.2	17.39
6.0	11.6	8.71	31.1	5.00	10.3	5.59	12.05
7.0	8.45	9.16	31.8	4.39	6.59	5.26	10.94
8.0	7.98	8.88	26.6	3.69	5.29	5.50	9.66
10.0	6.75	6.41	17.8	3.43	4.73	4.13	7.21
12.0	6.70	6.16	11.4	1.86	3.18	2.38	5.28

ND Not detected (<1.50 ng/ml)

TABLE 4

Plasma concentrations of pyridostigmine (Treatment B)
statistical analysis of data on Table 3

Time (hours)	Mean (ng/ml)	Maximum (ng/ml)	Minimum (ng/ml)	Standard deviation (ng/ml)	Coefficient of variation (%)
00	ND	ND	ND	-	-
0.25	1.15	3.68	ND	1.78	155
0.5	2.13	4.63	ND	2.34	110
0.75	5.25	9.62	2.41	2.90	55
1.0	6.81	12.2	3.08	3.39	50
1.3	12.48	28.7	5.73	8.69	70
1.7	15.15	35.8	6.95	11.27	74
2.0	17.24	43.4	3.11	14.52	84
2.5	19.78	44.2	7.79	13.69	69
3.0	22.76	51.4	8.56	15.60	69
3.5	22.61	48.5	9.09	13.54	60
4.0	21.02	41.7	10.3	10.97	52
5.0	17.39	39.5	7.55	11.36	65
6.0	12.05	31.1	5.00	9.68	80
7.0	10.94	31.8	4.39	10.38	95
8.0	9.66	26.6	3.69	8.51	88
10.0	7.21	17.8	3.43	5.35	74
12.0	5.28	11.4	1.86	3.60	68

ND Not detected (<1.50 ng/ml)

TABLE 5

Concentrations of pyridostigmine in plasma of dogs after single oral doses of 10 mg of the bromide salt as Formulation C

Results are expressed as ng/ml

Time (hours)	Subject number						
	1	2	3	4	5	6	Mean
00	ND	ND	ND	ND	ND	ND	ND
0.25	ND	5.01	ND	ND	ND	ND	-
0.5	ND	7.20	1.99	ND	ND	4.73	2.32
0.75	2.48	9.65	7.27	2.10	2.13	5.35	4.83
1.0	2.58	13.5	10.7	4.00	2.57	12.9	7.71
1.3	2.93	15.7	14.8	9.22	2.77	20.4	10.97
1.7	4.53	14.7	17.0	16.3	8.09	28.8	14.90
2.0	4.57	17.8	19.3	27.7	7.14	35.8	18.72
2.5	5.97	19.0	22.4	31.8	6.44	35.7	20.22
3.0	5.80	18.2	27.6	36.5	5.58	40.0	22.28
3.5	4.19	19.5	24.1	33.7	6.00	42.0	21.58
4.0	4.34	18.2	23.7	38.4	7.16	46.3	23.02
5.0	3.06	13.4	16.6	36.6	7.51	42.5	19.94
6.0	2.36	11.2	15.4	31.1	4.94	28.2	15.53
7.0	1.84	10.5	15.1	24.9	4.68	20.4	12.90
8.0	ND	8.34	13.9	19.5	3.45	18.4	10.60
10.0	ND	8.57	11.9	18.1	2.75	17.6	9.82
12.0	ND	7.07	7.66	12.9	ND	7.90	5.92

ND Not detected (<1.50 ng/ml)

TABLE 6

Plasma concentrations of pyridostigmine (Treatment C)
statistical analysis of data on Table 5

Time (hours)	Mean (ng/ml)	Maximum (ng/ml)	Minimum (ng/ml)	Standard deviation (ng/ml)	Coefficient of variation (%)
00	ND	ND	ND	-	-
0.25	ND	5.01	ND	-	-
0.5	2.32	7.20	ND	3.03	131
0.75	4.83	9.65	2.10	3.15	65
1.0	7.71	13.50	2.57	5.21	68
1.3	10.97	20.40	2.77	7.22	66
1.7	14.90	28.8	4.53	8.41	56
2.0	18.72	35.8	4.57	11.90	64
2.5	20.22	35.7	5.97	12.43	61
3.0	22.28	40.0	5.58	14.91	67
3.5	21.58	42.0	4.19	14.96	69
4.0	23.02	46.3	4.34	16.75	73
5.0	19.94	42.5	3.06	16.00	80
6.0	15.53	31.1	2.36	11.89	77
7.0	12.90	24.9	1.84	8.95	69
8.0	10.60	19.5	ND	7.99	75
10.0	9.82	18.1	ND	7.50	76
12.0	5.92	12.9	ND	5.04	85

ND Not detected (<1.50 ng/ml)

TABLE 7

Peak plasma concentration of pyridostigmine base and times of this occurrence after single oral doses of 10 mg of the bromide salt to dogs

Formulation / Subject	A		B		C	
	C max. (ng/ml)	T max. (hours)	C max. (ng/ml)	T max. (hours)	C max. (ng/ml)	T max. (hours)
1	28.7	4.0	21.9	4.0	6.0	2.5
2	23.6	3.0	16.3	3.5	19.5	3.5
3	17.2	3.0	51.4	3.0	27.6	3.0
4	26.2	3.0	10.3	4.0	38.4	4.0
5	26.0	4.0	28.9	3.0	8.1	1.7
6	7.0	3.5	21.2	3.5	46.3	4.0
Mean	21.5	3.4	25.0	3.5	24.3	3.1
SD	8.1	(3-4)a	14.3	(3-4)a	16.2	(1.7-4)a
CV (%)	38	-	57	-	67	-

SD Standard deviation
CV Coefficient of variation
a Range

TABLE 8

Areas under plasma pyridostigmine (base) concentration-time curves to 12 hours (AUC_{12})

Formulation / Subject	A (ng.h/ml)	B (ng.h/ml)	C (ng.h/ml)	Ratios		
				B/A	C/A	B/C
1	181.5	117.1	24.3	0.65	0.13	4.82
2	149.2	104.5	140.8	0.70	0.94	1.35
3	66.9	340.2	178.3	5.09	2.67	0.52
4	206.7	62.8	272.4	0.30	1.32	4.34
5	165.4	132.1	50.1	0.80	0.30	0.38
6	42.3	104.1	293.0	2.46	6.93	2.81
Mean	135.3	143.5	159.8	1.06[a]	1.18[a]	0.90[a]
SD	65.8	99.1	111.0	-	-	-
CV (%)	49	69	69	-	-	-

SD Standard deviation
CV Coefficient of variation
a Ratio of mean AUC_{12}

TABLE 9

Analysis of variance of peak plasma pyridostigmine concentrations
Logarithmic transformation to stabilise the variance

Source of variation	Degrees of freedom	Sums of squares	Mean square	Variance ratio	Significance level
Formulation	2	0.0780	0.0390	0.08	0.92(NS)
Subjects	5	0.6584	0.1317	0.28	0.91(NS)
Session	2	1.9828	0.9914	2.13	0.18(NS)
Residual	8	3.7256	0.4657	-	-
Total	17	6.4448	0.3791	-	-

NS Not significant (P>0.05)

Table of means (de-transformed data)

Formulation	A	B	C
Mean (ng/ml)	19.49	21.98	18.92

95% confidence intervals of formulation-related mean peak level ratios:

Ratio	B/A	C/A	B/C
95% Confidence interval	0.45, 2.80	0.39, 2.41	0.47, 2.89

TABLE 10

Analysis of variance of times to peak concentration
Logarithmic transformation to stabilise the variance

Source of variation	Degrees of freedom	Sums of squares	Mean square	Variance ratio	Significance level
Formulation	2	0.0780	0.0390	0.60	0.57(NS)
Subjects	5	0.1972	0.0395	0.61	0.70(NS)
Session	2	0.0143	0.0072	0.11	0.90(NS)
Residual	8	0.5170	0.0646	-	-
Total	17	0.8066	0.0475	-	-

NS Not significant (P>0.05)

Table of means (de-transformed data)

Formulation	A	B	C
Mean (hours)	3.39	3.48	2.99

95% confidence intervals of formulation-related mean time ratios:

Ratio	B/A	C/A	B/C
95% Confidence interval	0.73, 1.44	0.63, 1.24	0.83, 1.63

In addition, the mean times of the peak levels were not statistically significantly different (P>0.05) by a distribution-free sign test.

TABLE 11

Analysis of variance of AUC_{12}
Logarithmic transformation of data to stabilise the variance

Source of variation	Degrees of freedom	Sums of squares	Mean square	Variance ratio	P-value
Formulation	2	0.0142	0.0071	0.01	0.99(NS)
Subjects	5	1.0158	0.2032	0.32	0.89(NS)
Session	2	2.3939	1.1970	1.86	0.22(NS)
Residual	8	5.1397	0.6425	-	-
Total	17	8.5637	0.5037	-	-

NS Not significant (P>0.05)

Table of means (de-transformed data):

Formulation	A	B	C
Mean (ng.h/ml)	117.92	123.97	115.58

95% confidence intervals of formulation-related mean AUC_{12} ratios:

Ratio	B/A	C/A	B/C
95% Confidence interval	0.36, 3.06	0.34, 2.86	0.37, 3.13

FIGURE 2

Mean concentrations of pyridostigmine base in the plasma of dogs after single oral doses of 10 mg of the bromide salt as Formulations A(o-o), B(□-□) and C (Δ-Δ) Semi-logarithmic scale

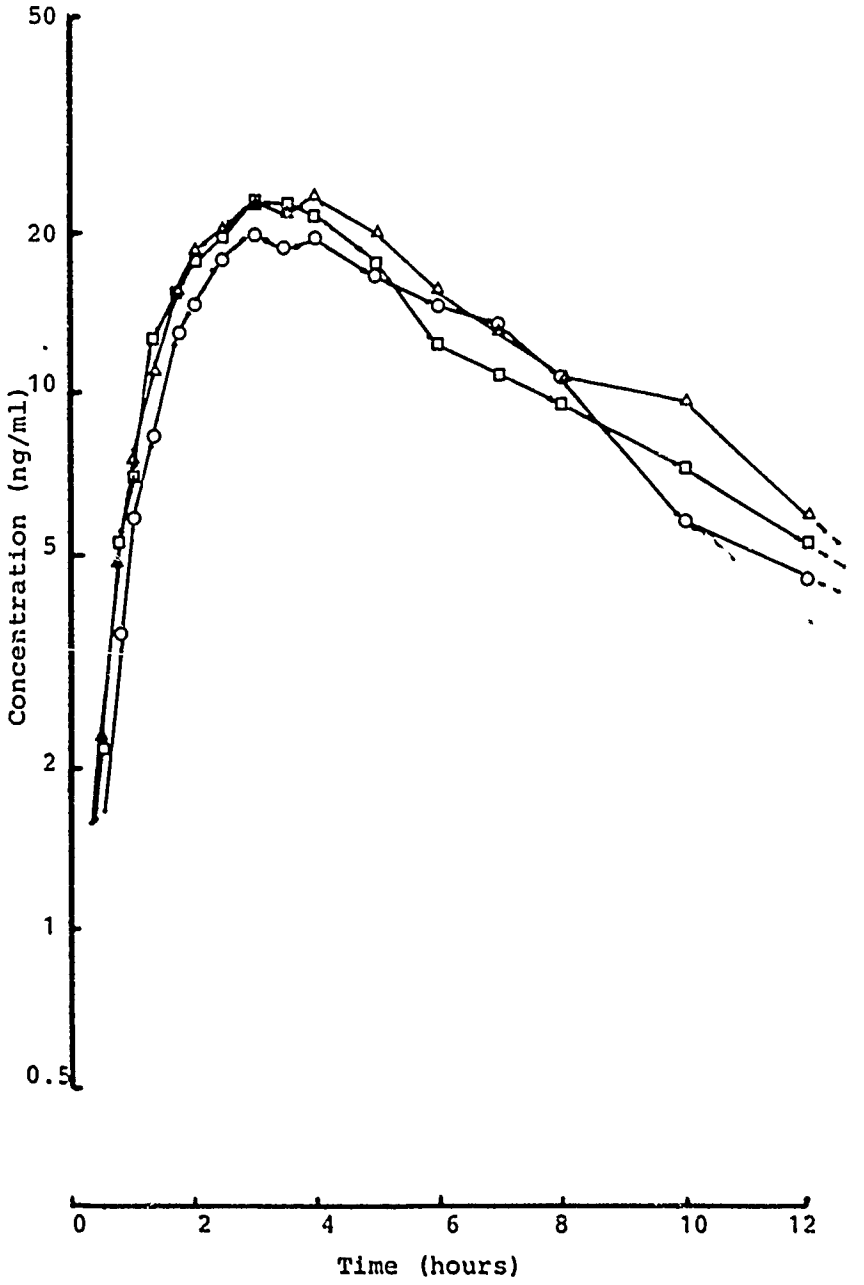


FIGURE 1

Mean concentration of pyridostigmine base in the plasma of dogs after single oral doses of 10 mg of the bromide salt as Formulations A (o-o), B(□-□) and C (Δ-Δ) linear scale

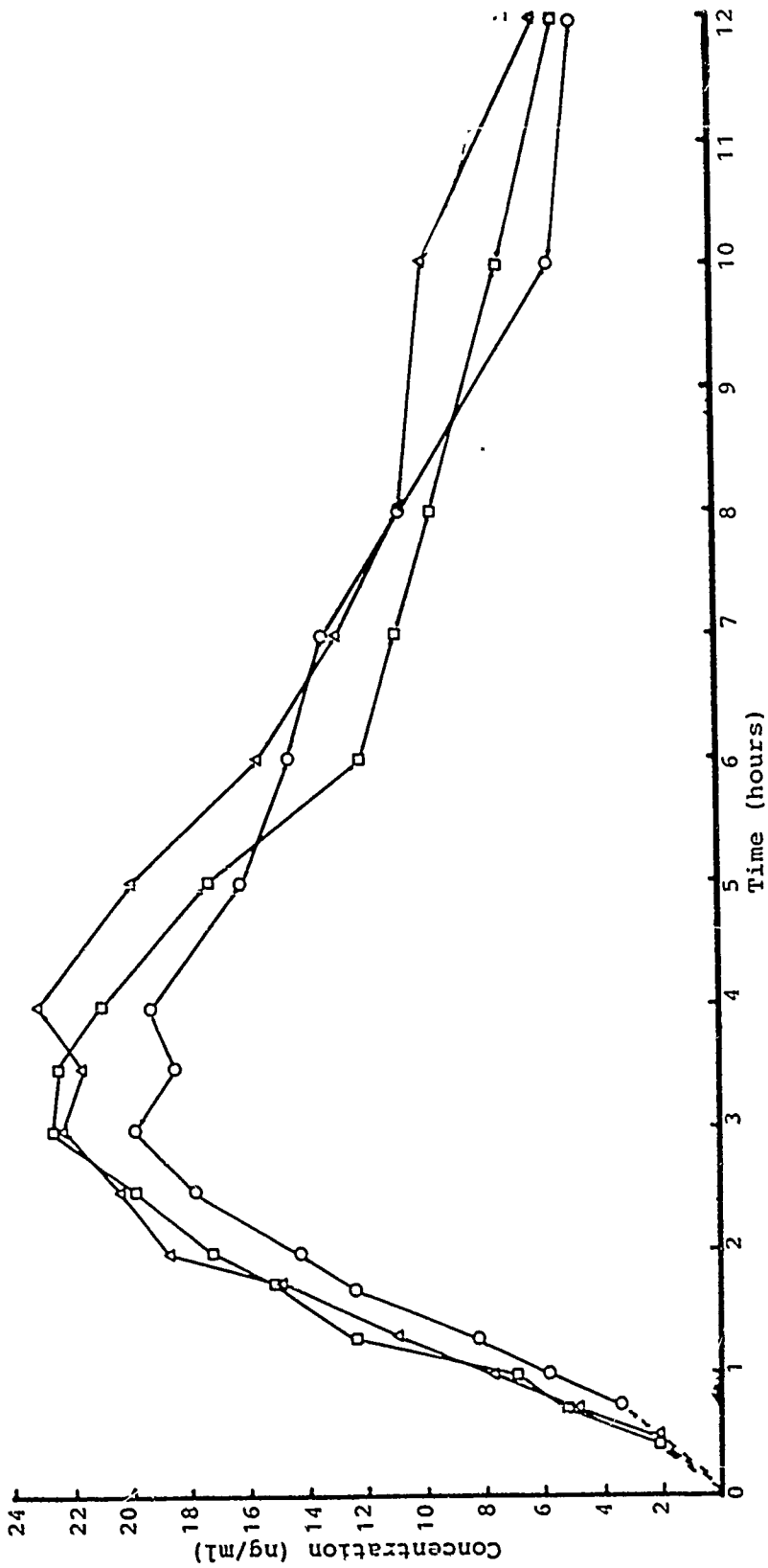


FIGURE 3

Concentrations of pyridostigmine base in the plasma of individual dogs after single oral doses of 10 mg of the bromide salt as Formulations A (o-o), B (□-□) and C (Δ-Δ)
Semi-logarithmic scale

Dog 1

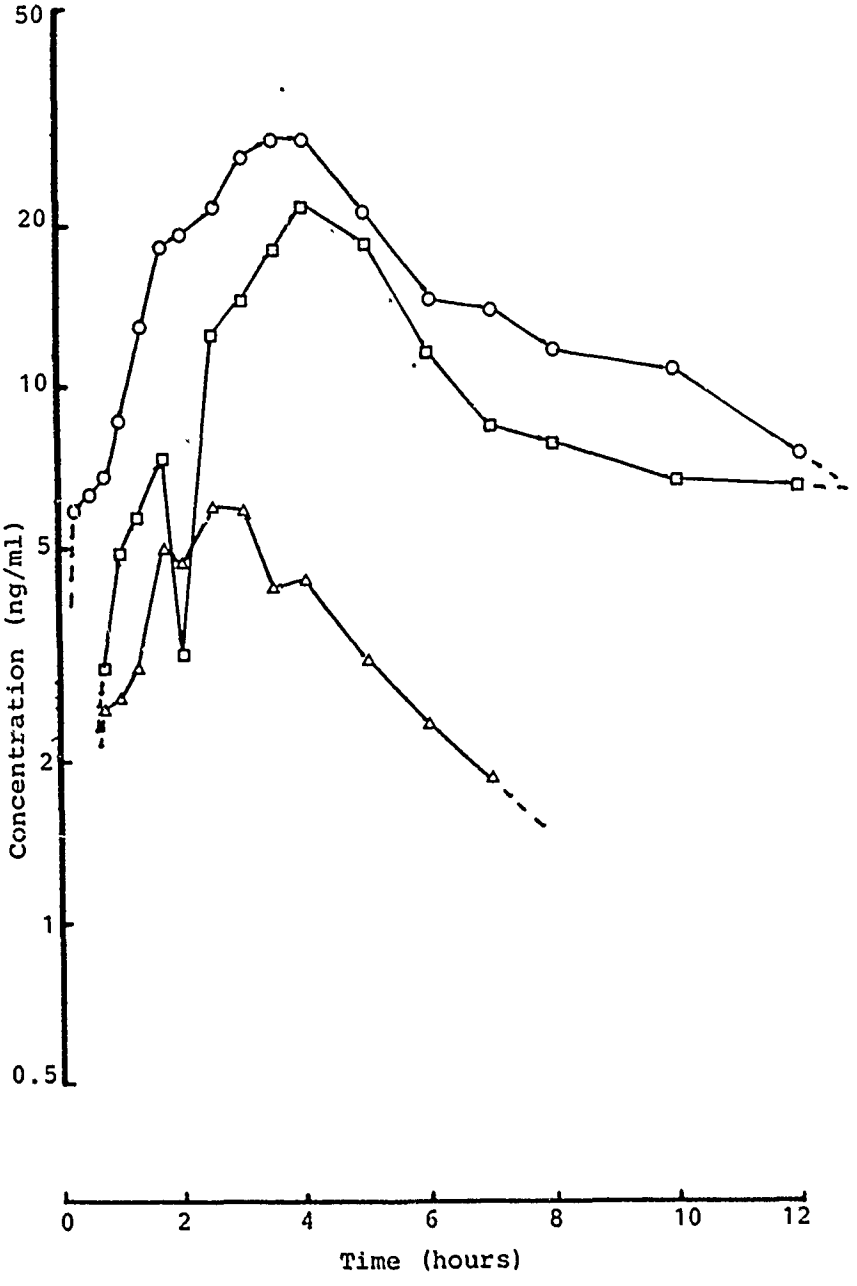


FIGURE 5

Concentrations of pyridostigimine base in the plasma of individual dogs after single oral doses of 10 mg of the bromide salt as Formulations A (o-o), B (□-□) and C (Δ-Δ)
Semi-logarithmic scale

Dog 3

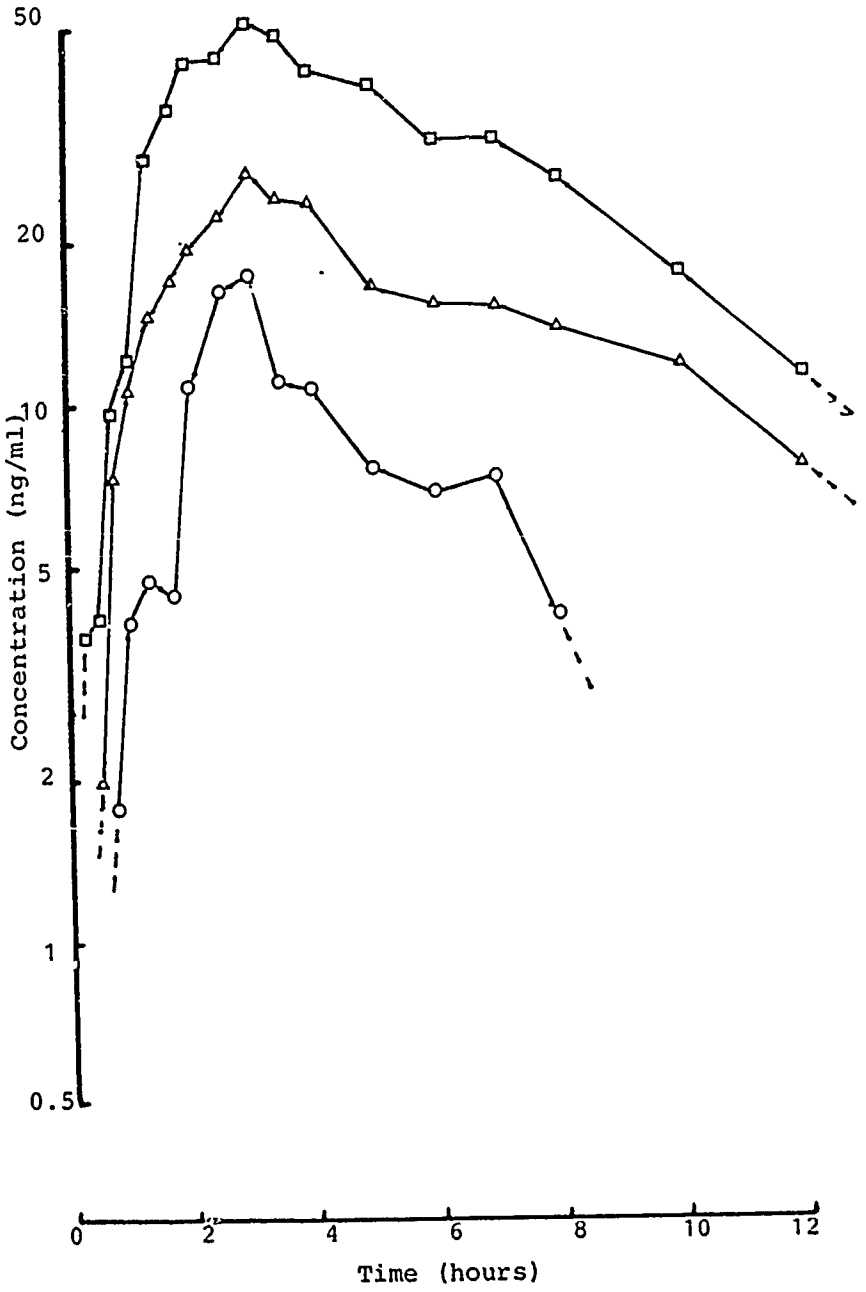


FIGURE 4

Concentrations of pyridostigmine base in the plasma of individual dogs after single oral doses of 10 mg of the bromide salt as Formulations A (o-o), B (□-□) and C (Δ-Δ)
Semi-logarithmic scale

Dog 2

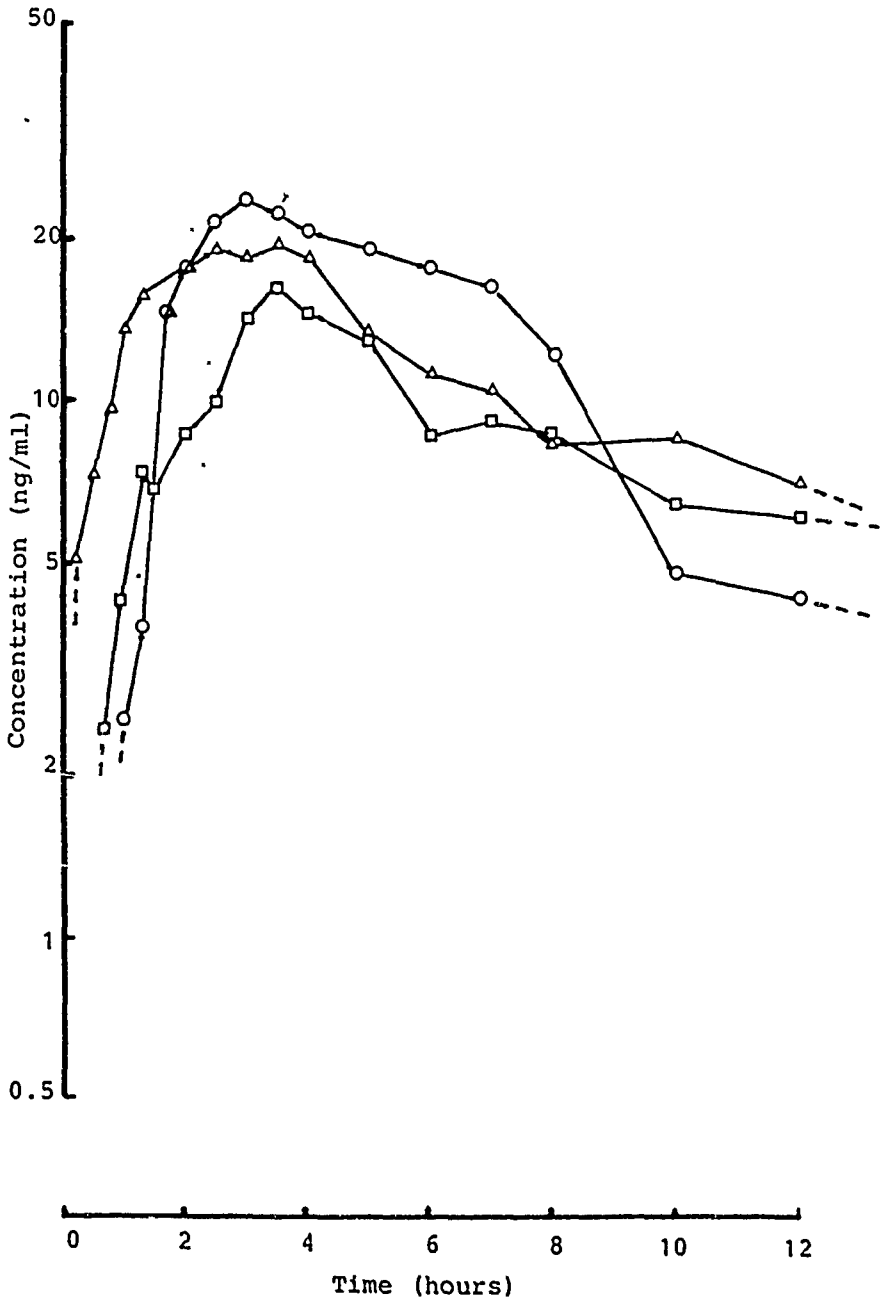


FIGURE 6

Concentrations of pyridostigmine base in the plasma of individual dogs after single oral doses of 10 mg of the bromide salt as Formulations A (o-o), B (□-□) and C (△-△)
Semi-logarithmic scale

Dog 4

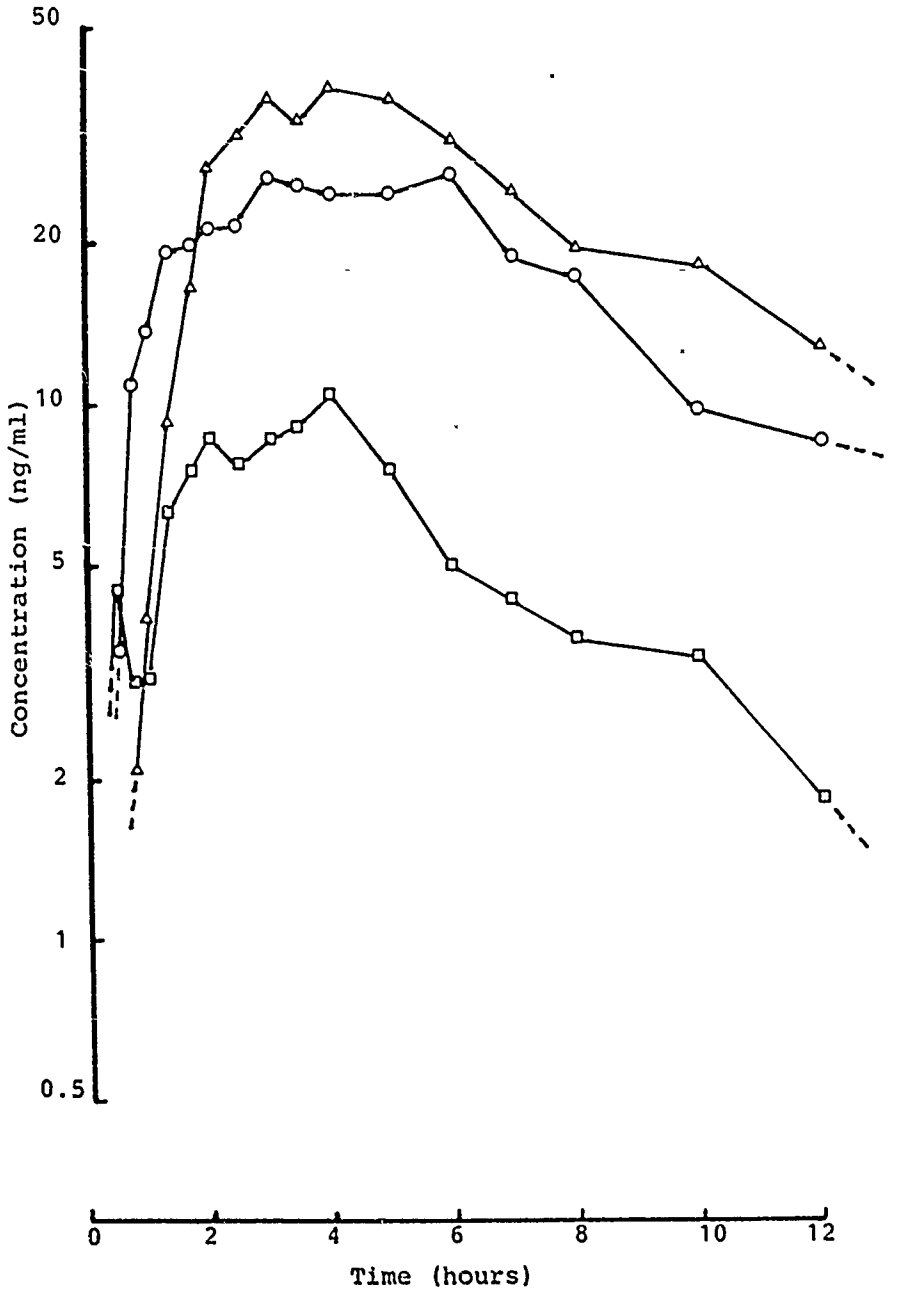


FIGURE 7

Concentrations of pyridostigmine base in the plasma of individual dogs after single oral doses of 10 mg of the bromide salt as Formulations A (o-o), B (□-□) and C (Δ-Δ)
Semi-logarithmic scale

Dog 5

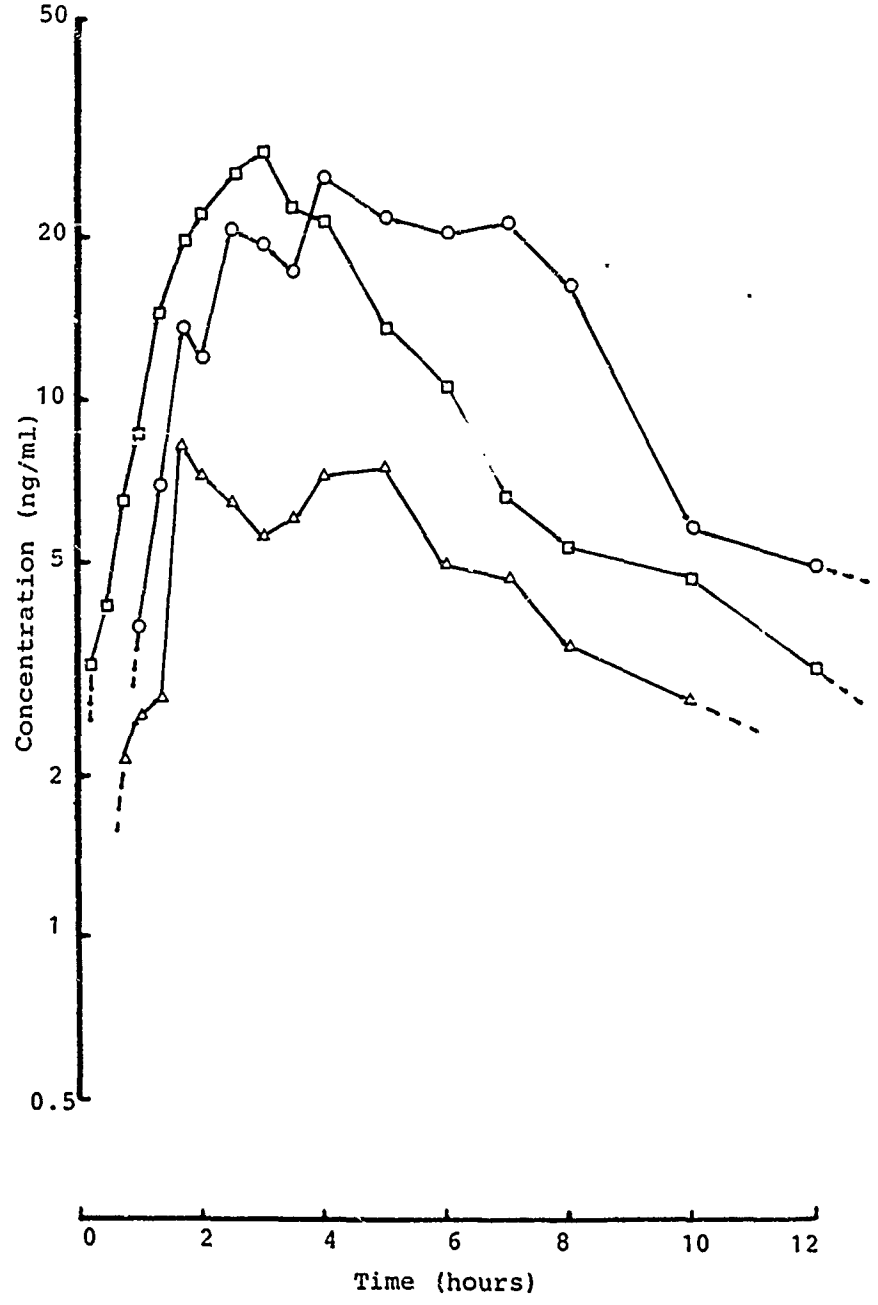
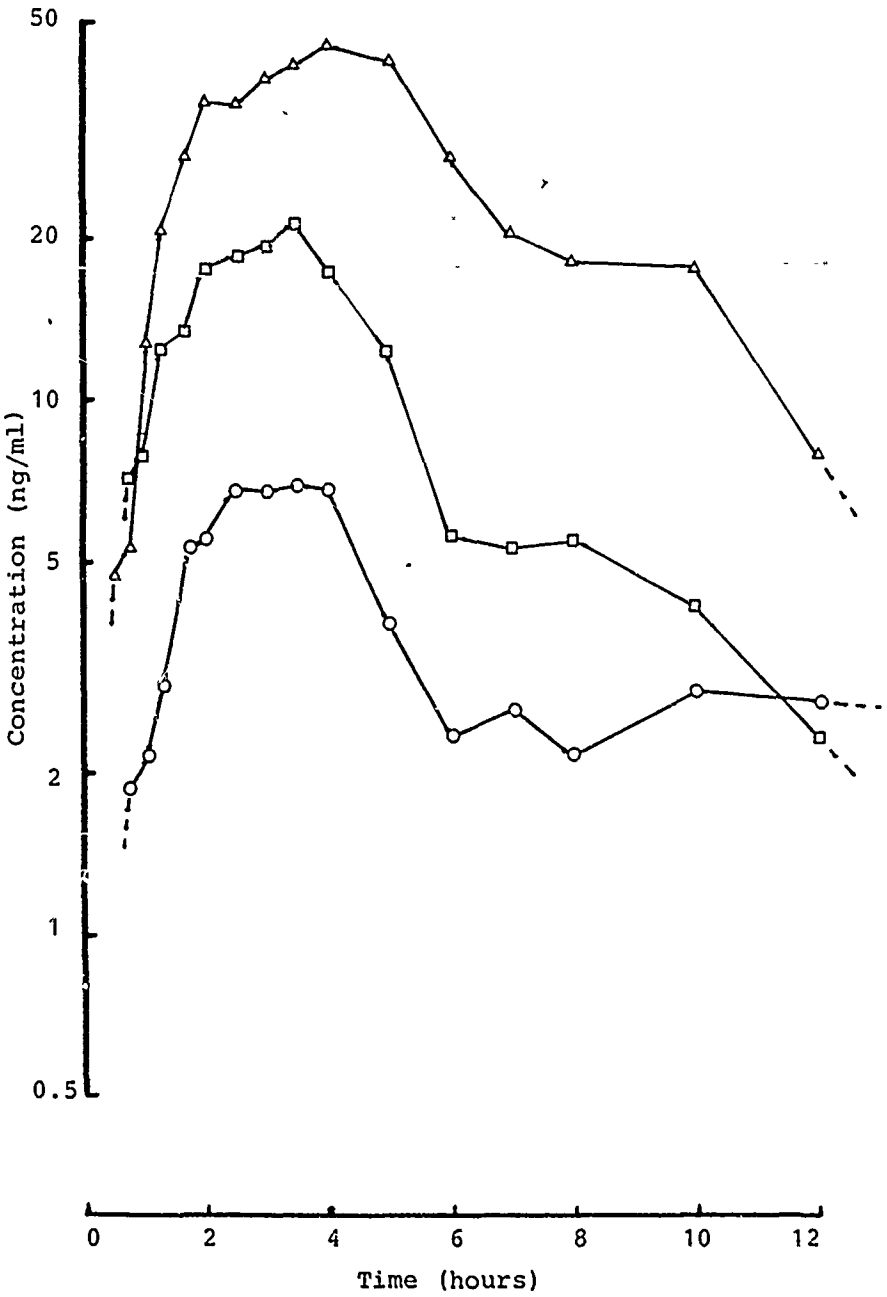


FIGURE 8

Concentrations of pyridostigmine base in the plasma of individual dogs after single oral doses of 10 mg of the bromide salt as Formulations A (o-o), B (□-□) and C (Δ-Δ)
Semi-logarithmic scale

Dog 6



BIOAVAILABILITY AND PHARMACOKINETICS OF PYRIDOSTIGMINE IN MALE BEAGLE DOGS AFTER ORAL AND INTRAVENOUS DOSES

SUMMARY

1. The pharmacokinetics of the cholinesterase inhibitor pyridostigmine in six male beagle dogs has been investigated after single intravenous doses of 6.94 mg (10 mg of the bromide salt) administered by constant-rate infusion during 0.25 hour and after single equal oral doses administered as a syrup and an extended-release tablet formulation.

2. After single intravenous infusion, mean concentrations of pyridostigmine base in plasma declined rapidly from 588 ng/ml ± 119 SD immediately after cessation of the infusion to 119 ng/ml ± 21 SD at 1 hour, and then more slowly to 3.0 ng/ml ± 1.3 SD at 24 hours. After oral doses of the syrup, mean concentrations of pyridostigmine in plasma were maintained at a relatively flat plateau during 2-4 hours after dosing, reaching a peak of 36.9 ng/ml ± 6.1 SD at 4 hours. Thereafter mean plasma drug concentrations declined slowly to 3.2 ng/ml ± 1.4 SD at 24 hours. After oral doses of the tablet, mean plasma drug concentrations increased to a peak level of 29.3 ng/ml ± 9.5 SD at 4 hours and thereafter declined to 2.3 ng/ml ± 2.1 SD at 24 hours.

The means of the peak concentrations of pyridostigmine in the plasma of individual dogs were 588 ng/ml ± 119 SD, 41.8 ng/ml ± 2.9 SD and 30.5 ng/ml ± 8.6 SD after single intravenous doses of 6.94 mg infused during 0.25 hours and after single equal oral doses as the syrup and tablet doses respectively, and the peak levels occurred at the end of infusion and mean times of 3.1 hours (range 2-4 hours) and 3.9 hours (range 2-5 hours) respectively.

3. Tri-exponential equations describing the decline of post-infusion plasma pyridostigmine concentrations with time provided satisfactory fits to the observed plasma level data and the coefficients of the fitted equations were transformed to those obtaining after bolus intravenous doses. Pharmacokinetic parameters of pyridostigmine were calculated from the transformed coefficients and exponents of these polyexponential equations without assuming a particular compartmental model. The systemic availability and the relative bioavailability of pyridostigmine from the oral dosage forms were estimated after deconvolution of the plasma drug concentration data after intravenous doses and the oral doses of the syrup and extended-release tablets.

4. After the oral doses, rates of availability to the systemic plasma were slow and very variable during up to 8-12 hours after dosing. During 24 hours, the mean systemic availability of pyridostigmine from the orally dosed syrup and tablets was 44.4% ± 4.3 SD and 33.6% ± 9.5 SD respectively of that from the intravenous dose. The mean relative bioavailability of pyridostigmine from the extended-release tablet was 76% (range 56%-112%) of that from the immediate-release syrup formulation. This difference was formally statistically significant ($P<0.05$). The data indicated that orally administered pyridostigmine was subject to pre-systemic elimination processes and the low relative bioavailability from the extended-release tablet was presumably related to incomplete release of drug from the tablet.

5. In male beagle dogs, pyridostigmine appeared to be a drug of relatively low systemic extraction ratio (mean 0.14 ± 0.01 SD) and systemic clearance (0.013 litres/minute/kg ± 0.001 SD) and of high volume of distribution ($V_{D(\lambda_z)}$, 8.7 litres/kg ± 1.9 SD; $V_{D(SS)}$, 3.9 litres/kg ± 0.9 SD). The mean residence time and mean (first pass) transit time of drug were 5.4 hours ± 1.5 SD and 0.8 hours ± 0.2 SD respectively. The ratio of the mean residence times of pyridostigmine in the plasma (sampling compartment) and the peripheral tissues respectively was 7.9, implying extensive tissue distribution of drug. After intravenous doses, pyridostigmine was rapidly distributed into peripheral tissues, achieving distribution equilibrium after about 3 hours. In the time taken to eliminate 6.94 mg (the dose), a mean total of 27.0 mg ± 5.3 SD was cumulatively transferred from the peripheral tissues back to the sampling compartment which included the plasma. Distribution processes, therefore, are a major determinant of the disposition of pyridostigmine in male beagle dogs.

TABLE 1

Concentrations[a] of pyridostigmine base in plasma after single intravenous infusion of 6.94 mg (10 mg of the bromide salt) during 0.25 hours (0.463 mg/minute) to dogs

Results are expressed as ng/ml

Time (hours)	Animal number						
	1	2	3	4	5	6	Mean
0[b]	628	691	638	413	692	465	588
0.08	246	354	248	287	354	370	310
0.25	157	259	142	182	202	203	191
0.5	135	204	116	134	171	159	153
1.0	103	121	100	104	146	142	119
1.5	85.2	102	84.8	91.5	129	104	99.4
3.0	62.4	75.8	52.5	57.5	72.5	57.5	63.0
4.0	31.7	29.4	40.6	30.0	59.1	43.6	39.1
5.0	26.1	41.6	25.4	23.2	38.7	27.2	30.4
6.0	20.9	31.6	21.7	19.3	31.2	20.4	24.2
7.0	16.9	24.7	19.2	17.8	21.3	18.5	19.7
8.0	14.3	18.1	22.8	14.3	19.0	13.2	17.0
10.0	10.7	14.9	14.8	12.0	10.4	9.77	12.1
12.0	7.75	9.79	11.4	10.1	8.68	6.02	8.96
14.0	6.77	9.34	6.80	7.74	7.78	3.70	7.02
16.0	3.36	6.44	4.79	6.23	6.46	3.09	5.06
24.0	1.96	5.01	2.54	3.86	2.71	1.67	2.96

[a] Data taken from Report No. PY-85-5-3 from the Dept. Pharmacy, University of California, San Francisco

[b] Sample taken at end of infusion (immediately before termination)

TABLE 2

Plasma concentrations of pyridostigmine
Statistical analysis of data on Table 1

Time (hours)	Maximum (ng/ml)	Minimum (ng/ml)	Mean (ng/ml)	Standard deviation (ng/ml)	Coefficient of variation (%)
0	692	413	588	119	20
0.08	370	246	310	56	18
0.25	259	142	191	41	22
0.5	204	116	153	32	21
1.0	146	100	119	21	17
1.5	129	84.8	99.4	16.6	17
3.0	75.8	52.5	63.0	9.2	15
4.0	59.1	29.4	39.1	11.4	29
5.0	41.6	23.2	30.4	7.7	25
6.0	31.6	19.3	24.2	5.6	23
7.0	24.7	16.9	19.7	2.9	15
8.0	22.8	13.2	17.0	3.7	22
10.0	14.9	9.77	12.1	2.3	19
12.0	11.4	6.02	8.96	1.90	21
14.0	9.34	3.70	7.02	1.88	27
16.0	6.46	3.09	5.06	1.55	31
24.0	5.01	1.67	2.96	1.26	43

TABLE 3

Concentrations[a] of pyridostigmine base in plasma after single oral doses of 6.94 mg (10 mg of the bromide salt) as a syrup to dogs

Results are expressed as ng/ml

Time (hours)	Animal number						
	1	2	3	4	5	6	Mean
0.25	26.3	ND	12.2	3.90	1.44	ND	7.31
0.5	28.1	3.11	32.1	9.25	ND	ND	12.1
1.0	33.2	9.22	33.1	24.9	2.25	13.0	19.3
1.5	38.3	20.2	37.7	32.5	19.9	29.3	29.7
2.0	36.5	24.5	41.5	37.8	34.7	44.5	36.6
2.5	36.5	27.3	35.8	35.8	41.6	35.3	35.4
3.0	37.3	29.2	37.6	34.9	46.2	35.6	36.8
3.5	39.7	29.7	34.2	35.0	35.5	27.3	33.6
4.0	33.3	39.4	37.8	39.7	44.3	26.6	36.9
5.0	24.4	33.1	26.1	25.0	40.6	24.2	28.9
6.0	26.6	27.1	22.3	21.1	28.1	23.5	24.8
7.0	21.6	21.5	24.2	15.8	24.3	18.5	21.0
8.0	20.7	19.0	20.2	16.6	20.4	12.5	18.2
10.0	14.7	11.2	15.8	12.7	13.9	6.93	12.5
12.0	9.38	7.55	10.3	7.65	12.0	4.82	8.62
14.0	6.33	5.43	9.17	6.47	8.35	4.54	6.72
16.0	6.85	5.26	7.42	5.10	7.65	5.39	6.28
24.0	2.79	2.67	5.94	3.22	2.22	2.25	3.18

a Data taken from Report No. PY-85-5-3 from the Dept. Pharmacy, University of California, San Francisco

ND Not detected (<1.42 ng/ml) ND values entered as zero for calculation of means

TABLE 4

Plasma concentrations of pyridostigmine
Statistical analysis of data on Table 3

Time (hours)	Maximum (ng/ml)	Minimum (ng/ml)	Mean (ng/ml)	Standard deviation (ng/ml)	Coefficient of variation (%)
0.25	26.3	ND	7.31	10.37	142
0.5	32.1	ND	12.1	14.4	119
1.0	33.2	2.25	19.3	13.0	68
1.5	38.3	19.9	29.7	8.2	28
2.0	44.5	24.5	36.6	6.9	19
2.5	41.6	27.3	35.4	4.6	13
3.0	46.2	29.2	36.8	5.5	15
3.5	39.7	27.3	33.6	4.4	13
4.0	44.3	26.6	36.9	6.1	17
5.0	40.6	24.2	28.9	6.6	23
6.0	28.1	21.1	24.8	2.9	12
7.0	24.3	15.8	21.0	3.3	16
8.0	20.7	12.5	18.2	3.2	18
10.0	15.8	6.93	12.5	3.2	25
12.0	12.0	4.82	8.62	2.50	29
14.0	9.17	4.54	6.72	1.75	26
16.0	7.65	5.10	6.28	1.16	18
24.0	5.94	2.22	3.18	1.40	44

ND Not detected (<1.42 ng/ml)

TABLE 5

Concentrations[a] of pyridostigmine base in plasma after single oral doses of 6.94 mg (10 mg of the bromide salt) as an extended-release tablet

Results are expressed as ng/ml

Time (hours)	Animal number						
	1	2	3	4	5	6	Mean
0.25	ND	ND	ND	1.85	1.86	ND	-
0.5	ND	ND	1.94	2.23	4.29	2.31	1.80
1.0	8.04	ND	7.42	8.90	9.54	11.9	7.63
1.5	16.8	11.9	10.9	16.1	13.1	13.9	13.8
2.0	20.9	21.7	12.6	18.0	16.2	24.0	18.9
2.5	26.1	28.8	15.1	20.3	21.3	22.0	22.3
3.0	28.5	35.7	18.3	18.5	24.0	23.5	24.8
3.5	31.1	34.6	24.1	22.8	23.8	22.3	26.5
4.0	45.5	35.7	26.3	22.5	24.9	20.6	29.3
5.0	19.0	36.3	21.1	16.6	28.2	16.4	22.9
6.0	19.9	27.9	17.2	16.8	18.6	12.2	18.8
7.0	17.6	23.8	21.9	14.9	16.8	10.4	17.6
8.0	15.5	20.4	16.2	12.4	16.3	8.53	14.9
10.0	9.20	14.0	8.62	8.26	13.2	5.45	9.79
12.0	5.81	9.71	8.97	9.60	8.04	2.82	7.49
14.0	4.81	7.77	6.57	8.12	5.71	2.04	5.84
16.0	3.93	7.40	6.22	8.83	4.47	1.70	5.42
24.0	1.44	4.20	3.42	4.80	ND	ND	2.31

a Data taken from Report No. PY-85-5-3 from the Dept. Pharmacy, University of California, San Francisco

ND Not detected (<1.42 ng/ml) ND values entered as zero for calculation of means

TABLE 6

Plasma concentrations of pyridostigmine
Statistical analysis of data on Table 5

Time (hours)	Maximum (ng/ml)	Minimum (ng/ml)	Mean (ng/ml)	Standard deviation (ng/ml)	Coefficient of variation (%)
0.25	1.86	ND	-	-	-
0.5	4.29	ND	1.80	1.62	90
1.0	11.9	ND	7.63	4.05	53
1.5	16.8	10.9	13.8	2.3	17
2.0	24.0	12.6	18.9	4.1	22
2.5	28.8	15.1	22.3	4.8	21
3.0	35.7	18.3	24.8	6.6	27
3.5	34.6	22.3	26.5	5.1	19
4.0	45.5	20.6	29.3	9.5	33
5.0	36.3	16.4	22.9	7.8	34
6.0	27.9	12.2	18.8	5.2	28
7.0	23.8	10.4	17.6	4.8	27
8.0	20.4	8.53	14.9	4.0	27
10.0	14.0	5.45	9.79	3.23	33
12.0	9.71	2.82	7.49	2.70	36
14.0	8.12	2.04	2.04	2.23	38
16.0	8.83	1.70	5.43	2.57	47
24.0	4.80	ND	2.31	2.12	92

ND Not detected (<1.42 ng/nl)

TABLE 7

Peak concentrations of pyridostigmine base in plasma and times of their occurrence after single doses of 6.94 mg (10 mg of the bromide salt) as an intravenous infusion during 0.25 hours and orally as a syrup and extended-release tablet formulations

Animal no.	Treatment					
	Intravenous infusion		Oral syrup		Oral tablet	
	Peak (ng/ml)	Time (hours)	Peak (ng/ml)	Time (hours)	Peak (ng/ml)	Time (hours)
1	628	0[a]	39.7	3.5	45.5	4
2	691	0[a]	39.4	4	36.3	5
3	638	0[a]	41.5	2	26.3	4
4	413	0[a]	39.7	4	22.8	3.5
5	692	0[a]	46.2	3	28.2	5
6	465	0[a]	44.5	2	24.0	2
Mean	588	0	41.8	3.1	30.5	3.9
SD	119	-	2.9	(2-4)[b]	8.8	(2-5)[b]
CV(%)	20	-	6.9	-	29	-

SD Standard deviation
CV Coefficient of variation
a Sample taken immediately before the infusion ceased
b Range

TABLE 8

Coefficients and exponents of the tri-exponential functions[a] fitted to post-infusion pyridostigmine plasma level data after intravenous infusion of 6.94 mg (10 mg of the bromide salt) during 0.25 hours to dogs

Animal no.	R_1 (ng/ml)	λ_1 $(hours)^{-1}$	R_2 (ng/ml)	λ_2 $(hours)^{-1}$	R_3 (ng/ml)	λ_3 $(hours)^{-1}$	Ratio $R_1:R_2:R_3$
1	463.36	20.4628	135.92	0.4884	27.17	0.1150	17:5:1
2	373.02	4.4996	142.76	0.4043	19.32	0.0602	19:7:1
3	487.17	19.2526	109.67	0.5384	40.07	0.1205	12:3:1
4	240.02	8.8625	151.44	0.5597	23.01	0.0761	10:7:1
5	479.63	15.2469	195.32	0.4065	19.85	0.0812	24:10:1
6	299.87	7.2677	170.55	0.3938	10.13	0.0771	30:17:1
Mean	390.51	12.5987	150.94	0.4652	23.26	0.0884	
SD	103.69	6.6499	29.50	0.0736	9.97	0.0239	
CV(%)	27	53	20	16	43	27	

Goodness-of-fit criteria

	Animal number					
Criterion	1	2	3	4	5	6
R^2[b]	0.9812	0.9419	0.9788	0.9908	0.9927	0.9897
variance accounted for (%)[c]	97.3	91.6	96.9	98.7	99.0	98.5

a The functions were of the form:
$C(t) = R_1e^{-\lambda_1.t} + R_2e^{-\lambda_2.t} + R_3e^{-\lambda_3.t}$
Where R_i, λ_i are constants and $\lambda_1>\lambda_2>\lambda_3$

b Square of the correlation coefficient, derived as the fractional reduction of sums of squares obtained by fitting the model

c Derived as the fractional reduction of residual mean squares obtained by fitting the model

SD Standard deviation

CV Coefficient of variation

TABLE 9

Coefficients and exponents of the fitted tri-exponential functions after transformation[a] of the coefficients to intravenous bolus dose conditions

Animal no.	A_1 (ng/ml)	λ_1 $(hours)^{-1}$	A_2 (ng/ml)	λ_2 $(hours)^{-1}$	A_3 (ng/ml)	λ_3 $(hours)^{-1}$	Ratio $A_1:A_2:A_3$
1	2384.72	20.4628	144.39	0.4884	27.56	0.1150	87:5:1
2	621.35	4.4996	150.10	0.4043	19.46	0.0602	32:8:1
3	2364.02	19.2526	117.22	0.5384	40.67	0.1205	58:3:1
4	596.91	8.8625	162.28	0.5597	23.22	0.0761	26:7:1
5	1869.55	15.2469	205.42	0.4065	20.05	0.0812	93:10:1
6	650.57	7.2677	179.08	0.3938	10.23	0.0771	64:18:1
Mean	1414.52	12.5987	159.75	0.4652	23.53	0.0884	
SD	886.69	6.6499	30.34	0.0736	10.16	0.0239	
CV(%)	63	53	19	16	43	27	

SD Standard deviation
CV Coefficient of variation
a The transformed functions were of the form:

$$C(t) = A_1e^{-\lambda_1 \cdot t} + A_2e^{-\lambda_2 \cdot t} + A_3e^{-\lambda_3 \cdot t}$$

Where A_i, λ_i are constants, $\lambda_1 > \lambda_2 > \lambda_3$ and:

$A_i = [R_i.T.\lambda_i]/[1-e^{-\lambda_i \cdot T}]$ where T is the infusion duration

TABLE 10

Areas under the plasma pyridostigmine concentration-time curves (AUC) and areas under the first moments of these curves (AUMC) after intravenous doses to dogs equivalent to bolus injection of 6.94 mg

Animal no.	A_1/λ_1		A_2/λ_2		A_3/λ_3		Total AUC (ng.h/ml)	Total AUMC ($ng.h^2/ml$)
	(ng.h/ml)	(% of total)	(ng.h/ml)	(% of total)	(ng.h/ml)	(% of total)		
1	116.5	17.9	295.6	45.4	239.7	36.8	651.8	2694.9
2	138.1	16.6	371.3	44.6	323.3	38.8	832.6	6318.7
3	122.8	18.1	217.7	32.1	337.5	49.8	678.0	3211.7
4	67.4	10.2	289.9	43.8	305.1	46.1	662.4	4535.2
5	122.6	14.0	505.3	57.8	246.9	28.2	874.9	4292.1
6	89.5	13.2	454.7	67.2	132.7	19.6	676.9	2888.0
Mean	109.5	15.0	355.8	48.5	264.2	36.6	729.4	3990.1
SD	26.0	3.1	109.0	12.3	75.8	11.2	97.7	1364.5
CV(%)	24	21	31	25	29	31	13	34

SD Standard deviation
CV Coefficient of variation

TABLE 11

Volumes of distribution of pyridostigmine in dogs

Animal no.	V_P[a]		$V_{D(\lambda_3)}$[b]		$V_{D(SS)}$[c]	
	(litres)	(litres/kg)	(litres)	(litres/kg)	(litres)	(litres/kg)
1	2.71	0.19	92.58	6.61	44.02	3.14
2	8.77	0.69	138.46	10.82	63.26	4.94
3	2.75	0.22	84.94	6.80	48.48	3.88
4	8.87	0.64	137.67	9.98	71.73	5.20
5	3.31	0.27	97.69	7.82	38.92	3.11
6	8.26	0.64	132.97	10.23	43.74	3.36
Mean	5.78	0.44	114.05	8.71	51.69	3.94
SD	3.14	0.24	24.85	1.86	12.89	0.92
CV(%)	54	54	22	21	25	23

SD Standard deviation
CV Coefficient of variation
a Volume of sampling compartment which includes the plasma
b Volume of distribution after attainment of distribution equilibrium
c Volume of distribution at steady-state

TABLE 12

Mean residence times of pyridostigmine in dogs after intravenous doses

Results are expressed as hours

Animal no.	MRT[a]	$MRT_{(p)}$[b]	$MRT_{(t)}$[c]	MTT[d]	Ratio $MRT_{(t)}/MRT_{(p)}$
1	4.13	0.25	3.88	0.68	15.5
2	7.59	1.05	6.54	1.04	6.2
3	4.74	0.27	4.47	0.85	16.6
4	6.85	0.85	6.00	1.12	7.1
5	4.91	0.42	4.49	0.65	10.7
6	4.27	0.81	3.46	0.73	4.3
Mean	5.42	0.61	4.81	0.85	7.9[e]
SD	1.45	0.34	1.21	0.20	-
CV(%)	27	56	25	23	-

SD Standard deviation
CV Coefficient of variation
a Mean residence time in body
b Mean residence time in sampling compartment (plasma)
c Mean residence time in peripheral tissues
d Mean (first pass) transit time
e Ratio of mean data

TABLE 13

Calculated time course of rates of transfer[a] of pyridostigmine from the sampling compartment including the plasma after (transformation to) bolus intravenous doses of 6.94 mg (10 mg of the bromide salt) to dogs

Results are expressed as mg/hour; at times corresponding to those of blood sampling after the dose administered by infusion

Time (hours)	Animal no.						Mean (± SD)
	1	2	3	4	5	6	
0.00	132.66	25.08	125.42	47.74	94.71	39.66	77.54 (46.26)
0.08	32.70	18.97	32.79	28.80	34.85	25.85	28.99 (5.88)
0.25	8.76	11.31	8.01	13.97	11.15	13.13	11.06 (2.34)
0.50	7.22	6.56	6.37	9.28	8.49	8.22	7.69 (1.16)
1.00	5.87	3.98	5.20	6.98	7.02	6.17	5.87 (1.15)
1.50	4.80	3.18	4.29	5.54	5.85	5.11	4.80 (0.96)
3.00	2.74	1.93	2.57	2.98	3.45	2.98	2.77 (0.51)
3.50	2.31	1.66	2.21	2.48	2.92	2.50	2.35 (0.42)
4.00	1.96	1.43	1.93	2.10	2.48	2.10	2.00 (0.34)
5.00	1.46	1.09	1.50	1.57	1.82	1.51	1.49 (0.24)
6.00	1.12	0.85	1.21	1.24	1.37	1.10	1.15 (0.17)
7.00	0.88	0.69	1.00	1.03	1.05	0.82	0.91 (0.14)
8.00	0.72	0.57	0.85	0.88	0.83	0.62	0.75 (0.13)
10.00	0.51	0.42	0.63	0.70	0.56	0.39	0.54 (0.12)
12.00	0.38	0.34	0.49	0.58	0.41	0.27	0.41 (0.11)
14.00	0.29	0.28	0.38	0.49	0.32	0.20	0.33 (0.10)
16.00	0.23	0.24	0.30	0.42	0.26	0.16	0.27 (0.09)
24.00	0.09	0.15	0.11	0.23	0.13	0.08	0.13 (0.05)
Transfer ("elimination") function (q; $hour^{-1}$)	19.115	3.613	18.072	6.880	13.647	5.714	11.174 (6.666)

[a] Rates of removal ("elimination") from the sampling compartment. Includes irreversible elimination and transfer to tissues. Calculated as Vp.q.C(t), when Vp is the apparent volume of the sampling compartment, q is the transfer function ("elimination") from the sampling compartment by all routes) and C(t) is the plasma drug concentration at time t

TABLE 14

Calculated time course of rates of transfer[a] of pyridostigmine from peripheral tissues to the sampling compartment after (transformation to) bolus intravenous doses of 6.94 mg (10 mg of the bromide salt) to dogs

Results are expressed as mg/hour at times corresponding to those of blood sampling after the dose administered by infusion

Time (hours)	Animal no.						Mean (± SD)
	1	2	3	4	5	6	
0	0	0	0	0	0	0	
0.08	6.69	1.26	5.72	4.73	6.57	3.28	4.71 (2.11)
0.25	7.91	2.85	6.93	8.17	8.90	6.26	6.84 (2.16)
0.5	7.14	3.53	6.28	8.12	8.28	6.71	6.68 (1.73)
1	5.77	3.34	5.11	6.50	6.87	5.75	5.56 (1.25)
1.5	4.71	2.85	4.21	5.18	5.72	4.79	4.58 (0.98)
3[b]	-	-	-	-	-	-	-

Transfer (distribution) function h(t)

$$h(t) = G_1 e^{-\gamma_1 . t} + G_2 e^{-\gamma_2 . t} \quad (hours^{-2})$$

Animal no.	G_1 ($hours^{-2}$)	γ_1 ($hours^{-1}$)	G_2 ($hours^{-2}$)	γ_2 ($hours^{-1}$)
1	24.98	1.7868	0.20	0.1640
2	2.85	1.2594	0.04	0.0915
3	20.41	1.6313	0.38	0.2058
4	12.57	2.4903	0.08	0.1283
5	21.17	1.9819	0.06	0.1060
6	8.27	1.9321	0.02	0.0921

a Rates of return (distribution) from the peripheral tissues to the sampling compartment. Calculated as V_p. C(t)*h(t) where V_p is the apparent volume of the sampling compartment

b At later times the rate of transfer approached the rate of transfer from the sampling compartment (Table 13)

TABLE 15

Clearance and extraction ratios of pyridostigmine

Animal no.	Systemic clearance (Cl_s)		Terminal[a] half-life (hours)	"Elimination transfer"[b] clearance (Cl_e)		"Distribution transfer"[c] clearance (Cl_d)		Systemic[d] extraction ratio (E_s)	Hepatic[e] extraction ratio (E_h)
	(litres/min)	(litres/min/kg)		(litres/min)	(litres/min/kg)	(litres/min)	(litres/min/kg)		
1	0.177	0.013	6.0	0.865	0.062	0.687	0.049	0.141	0.56
2	0.139	0.011	11.5	0.518	0.040	0.379	0.030	0.121	0.48
3	0.171	0.014	5.8	0.838	0.067	0.667	0.053	0.152	0.61
4	0.175	0.013	9.1	1.006	0.073	0.831	0.060	0.141	0.56
5	0.132	0.011	8.5	0.748	0.060	0.616	0.049	0.118	0.47
6	0.171	0.013	9.0	0.755	0.058	0.585	0.045	0.146	0.58
Mean	0.161	0.013	8.3	0.788	0.060	0.628	0.048	0.137	0.54
SD	0.020	0.001	2.1	0.162	0.011	0.148	0.010	0.014	-
CV(%)	12	10	26	21	19	24	21	10	-

SD Standard deviation
CV Coefficient of variation
a Calculated as $(\log_e 2)/\lambda_3$
b Clearance associated with drug transfer from sampling compartment (both reversible and irreversible)
c Clearance associated with drug transfer from peripherals to the sampling compartment
d Calculated as Cl_s/Q, where Q is the cardiac plasma output (taken as 90 ml/min/kg)
e Calculated approximately as $\mu.E_s$, where μ is the fraction of the cardiac output supplying the liver (taken as 25%) and assuming the liver to be the sole eliminating organ

TABLE 16

Cumulative mass transfer of pyridostigmine between the sampling compartment and peripheral tissues

Results are expressed as mg

Animal no.	Amount transferred[a]		
	From sampling compartment[b]	From peripheral to sampling compartment	Amount eliminated
1	33.82	26.88	6.94
2	25.86	18.92	6.94
3	34.07	27.13	6.94
4	39.98	33.04	6.94
5	39.27	32.33	6.94
6	30.69	23.75	6.94
Mean	33.95	27.01	6.94
SD	5.31	5.31	-
CV(%)	16	20	-

SD Standard devation
CV Coefficient of variation
a Cumulative amounts transferred during the total residence time of drug in the body
b Including both distribution and irreversible elimination processes. For each animal, the numerical difference of the two columns represents the cumulative amount eliminated (i.e. the dose)

TABLE 17

Calculated fractional input rates[a] and cumulative availability[b] of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in a syrup) to dogs

Results are presented at times equivalent to those of blood sampling. Standard deviations in parentheses

Time (hours)	Animal no.													
	1		2		3		4		5		6		Mean	
	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)
0.25	0.077	1.93	c	0	0.036	0.91	0.031	0.77	0.005	0.12	c	0	0.025	0.75 (0.77)
0.5	0.074	3.77	0.022	0.54	0.092	3.20	0.062	2.31	c	(0.10)	c	0	0.042	1.65 (1.65)
1.0	0.076	7.31	0.043	2.36	0.077	7.50	0.134	8.22	0.007	0.27	0.079	2.86	0.069	4.75 (3.33)
1.5	0.079	11.31	0.083	6.12	0.080	11.36	0.126	14.70	0.060	2.59	0.135	8.90	0.094	9.16 (4.30)
2.0	0.064	14.71	0.072	9.89	0.081	15.52	0.121	20.89	0.089	6.81	0.161	17.11	0.098	14.16 (5.07)
2.5	0.059	17.71	0.070	13.40	0.058	18.67	0.079	25.33	0.089	11.24	0.052	20.91	0.068	17.88 (5.09)
3.0	0.058	20.60	0.064	16.76	0.060	21.64	0.070	28.90	0.084	15.64	0.062	23.90	0.066	21.24 (4.85)
3.5	0.062	23.70	0.061	19.64	0.048	24.17	0.072	32.36	0.038	18.00	0.010	24.96	0.049	23.81 (5.01)
4.0	0.041	26.05	0.104	24.44	0.058	26.92	0.099	37.11	0.068	20.91	0.030	26.13	0.067	26.93 (5.43)
5.0	0.022	28.53	0.036	30.76	0.023	30.77	0.001	40.64	0.042	26.82	0.027	29.14	0.025	31.11 (4.90)
6.0	0.033	31.46	0.026	33.55	0.020	32.53	0.023	42.00	0.012	28.82	0.032	32.29	0.024	33.44 (4.49)
7.0	0.021	34.01	0.014	35.27	0.029	35.19	0.007	43.18	0.016	30.21	0.012	34.29	0.017	35.36 (4.26)
8.0	0.022	36.11	0.016	36.81	0.018	37.47	0.027	45.82	0.012	31.61	c	34.56	0.016	37.06 (4.77)
10.0	0.011	39.48	c	38.10	0.013	40.37	0.007	48.61	0.007	33.30	0.002	34.57	0.007	39.07 (5.43)
12.0	0.004	40.81	0.001	38.21	0.004	41.90	c	48.81	0.009	35.04	0.003	35.04	0.004	39.97 (5.18)
14.0	0.002	41.38	0	38.32	0.006	42.94	0.003	49.21	0.003	36.14	0.006	35.86	0.003	40.64 (5.05)
16.0	0.007	42.32	0.004	38.76	0.004	44.05	c	49.53	0.006	37.05	0.008	37.34	0.005	41.51 (4.82)
24.0	c	46.61	c	40.67	0.006	47.61	0.002	50.17	c	39.90	c	41.45	-	44.40 (4.27)

[a] Rate at the mid-point of the immediately preceeding 0.25 hour interval, e.g. the rate 0.064 $hour^{-1}$ at 2 hours (animal 1) is actually that at 1.875 hours

[b] Cumulative availability at the end of the stated time

[c] Calculated rates were zero, or negative due to instabilities in the calculation

TABLE 18

Calculated fractional input rates[a] and cumulative availability[b] of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in an extended-release tablet) to dogs

Results are presented at times equivalent to those of blood sampling. Standard deviations in parentheses

Time (hours)	Animal no.													
	1		2		3		4		5		6		Mean	
	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)	Input rate ($hours^{-1}$)	Cumulative availability (% dose)
0.25	0	0	0	0	0	0	0.015	0.37	0.006	0.16	0	0	-	- -
0.5	0	0	0	0	0.006	0.14	0.012	0.67	0.013	0.50	0.017	0.41	0.008	0.29 (0.28)
1.0	0.023	0.79	0	0	0.020	0.98	0.053	2.69	0.026	1.65	0.061	3.12	0.031	1.54 (1.19)
1.5	0.042	2.71	0.066	2.52	0.027	2.26	0.074	6.30	0.030	3.13	0.047	5.51	0.048	3.74 (1.72)
2.0	0.047	5.01	0.084	6.58	0.027	3.62	0.059	9.42	0.033	4.73	0.090	9.63	0.057	6.50 (2.53)
2.5	0.055	7.64	0.093	11.08	0.031	5.13	0.059	12.44	0.043	6.75	0.044	12.39	0.054	9.24 (3.14)
3.0	0.054	10.40	0.101	16.16	0.037	6.89	0.037	14.44	0.043	8.93	0.050	14.79	0.054	11.94 (3.72)
3.5	0.056	13.08	0.069	19.97	0.049	9.21	0.066	17.39	0.036	10.79	0.034	16.74	0.052	14.53 (4.17)
4.0	0.091	17.27	0.071	23.47	0.050	11.75	0.048	20.10	0.036	12.54	0.026	18.12	0.054	17.21 (4.47)
5.0	0.005	21.43	0.058	30.07	0.028	15.49	0.017	22.48	0.038	16.52	0.012	19.86	0.026	20.98 (5.22)
6.0	0.021	22.35	0.022	33.39	0.019	17.51	0.030	25.06	0.008	18.38	0.006	20.55	0.018	22.87 (5.83)
7.0	0.017	24.45	0.021	35.47	0.033	20.39	0.019	27.47	0.013	19.34	0.009	21.32	0.019	24.74 (6.04)
8.0	0.015	25.97	0.016	37.30	0.015	22.70	0.012	28.92	0.015	20.82	0.006	22.03	0.013	26.29 (6.15)
10.0	0.004	27.80	0.007	39.42	0.003	23.71	0.006	30.24	0.010	23.37	0.002	22.81	0.005	27.89 (6.36)
12.0	0.002	28.26	0.003	40.34	0.009	25.07	0.016	32.86	0.002	24.40	c	22.84	0.005	28.96 (6.61)
14.0	0.003	28.79	0.004	41.07	0.004	26.28	0.008	35.00	0.002	24.83	0.001	22.91	0.004	29.81 (6.92)
16.0	0.002	29.32	0.006	42.14	0.005	27.18	0.014	37.32	0.002	25.29	0.001	23.14	0.005	30.73 (7.42)
24.0	c	30.43	c	45.51	0.002	31.06	c	45.13	c	25.76	c	23.37	-	33.54 (9.56)

[a] Rate at the mid-point of the immediately preceeding 0.25 hour interval, e.g. the rate 0.047 $hour^{-1}$ at 2 hours (animal 1) is actually that at 1.875 hours

[b] Cumulative availability at the end of the stated time

[c] Calculated rates were zero or negative due to instabilities in the calculation

TABLE 19

Systemic availability and relative bioavailability of pyridostigmine derived by deconvolution after single oral doses of 6.94 mg (10 mg of the bromide salt) in a syrup and an extended-release tablet to dogs

Results are expressed as % dose during 24 hours

Animal no.	Syrup (B)	Tablet (C)	Ratio C/B	Hepatic extraction ratio (E_h)	
				(a)	(b)
1	46.6	30.4	0.65	0.53	0.56
2	40.7	45.5	1.12	0.59	0.48
3	47.6	31.1	0.65	0.52	0.61
4	50.2	45.1	0.90	0.50	0.56
5	39.9	25.8	0.65	0.60	0.47
6	41.5	23.4	0.56	0.59	0.58
Mean	44.4	33.6	0.76[c]	0.56	0.54
SD	4.3	9.5	-	-	-
CV(%)	10	28	-	-	-

SD Standard deviation
CV Coefficient of variation
a Calculated as 1-F, when F is the systemic availability after the oral doses of the syrup
b From Table 15, calculated from the systemic extraction ratio
c Ratio of mean data

FIGURE 1

Mean concentrations of pyridostigmine base in plasma of dogs after single doses of 6.94 mg (10 mg of the bromide salt) as an intravenous infusion during 0.25 hours (o-o), as a syrup administered orally (●-●) and as extended-release tablets administered orally (■-■). Semi-logarithmic scale

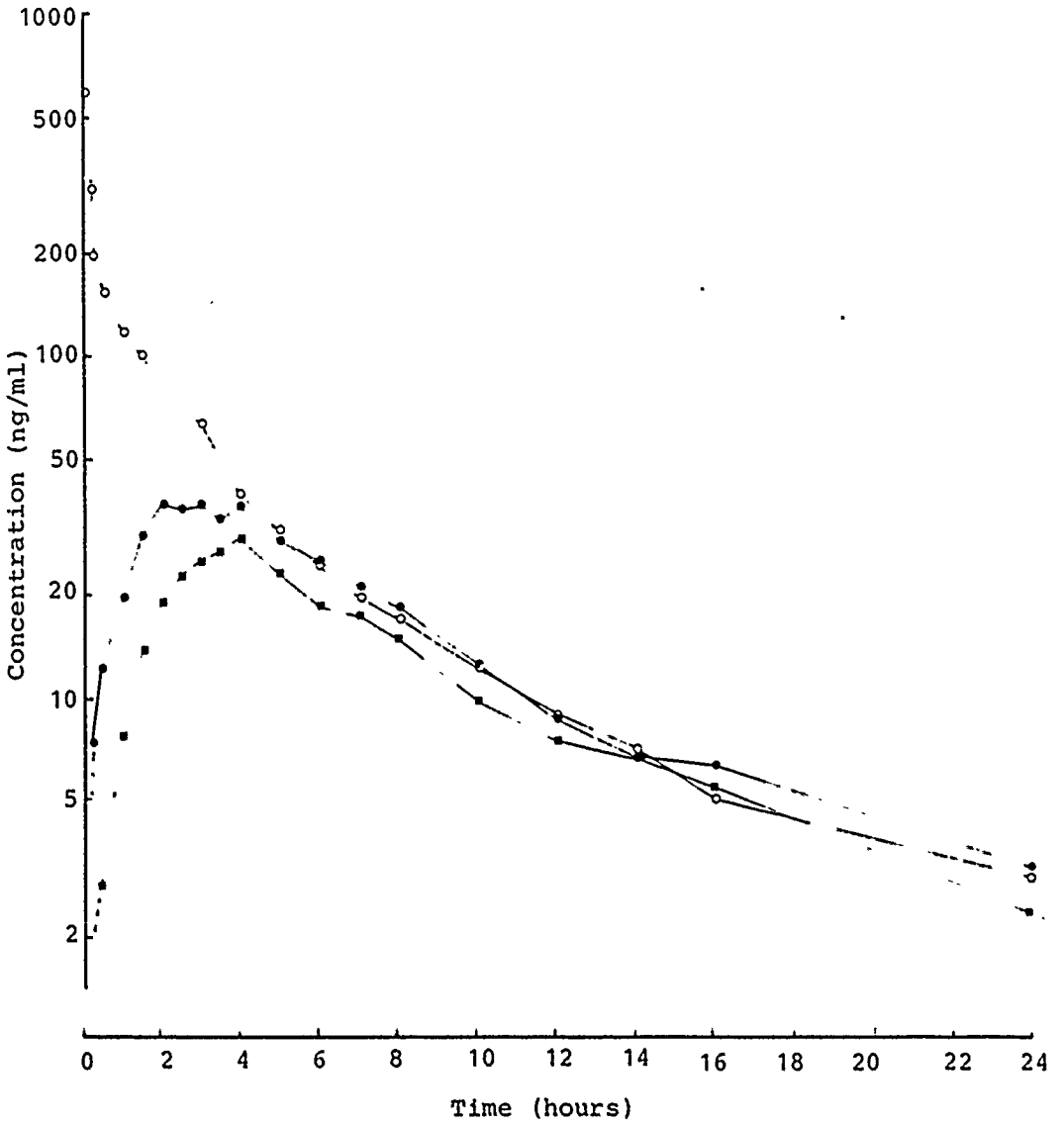


FIGURE 2

Measured plasma concentrations of pyridostigmine base (* - *) and concentrations calculated from a tri-exponential equation (solid line) fitted by non-linear regression after single intravenous infusion of 6.94 mg during 0.25 hours

Animal 1

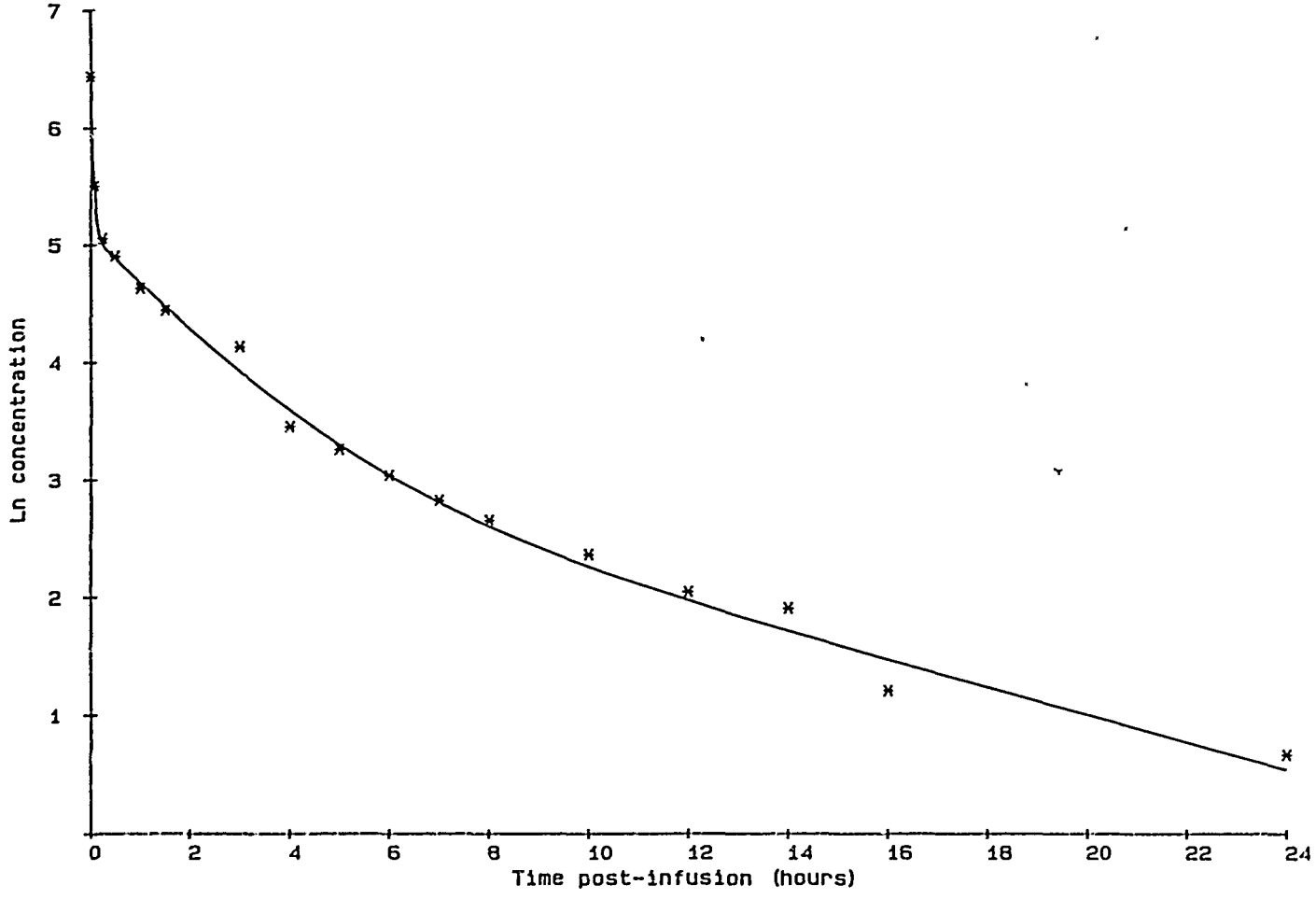


FIGURE 3

Measured plasma concentrations of pyridostigmine base (* - *) and concentrations calculated from a tri-exponential equation (solid line) fitted by non-linear regression after single intravenous infusion of 6.94 mg during 0.25 hours

Animal 2

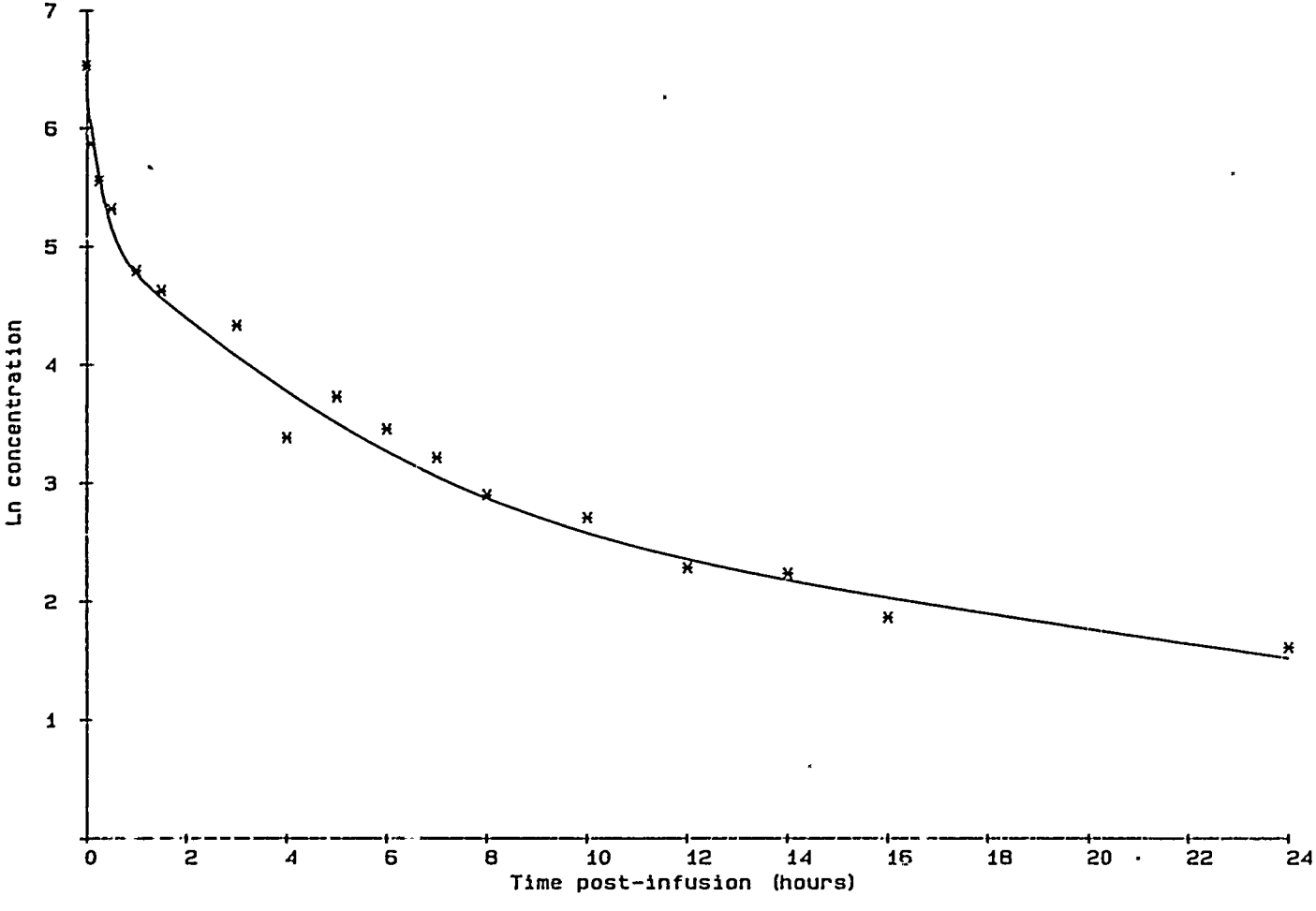


FIGURE 4

Measured plasma concentrations of pyridostigmine base (* - *) and concentrations calculated from a tri-exponential equation (solid line) fitted by non-linear regression after single intravenous infusion of 6.94 mg during 0.25 hours

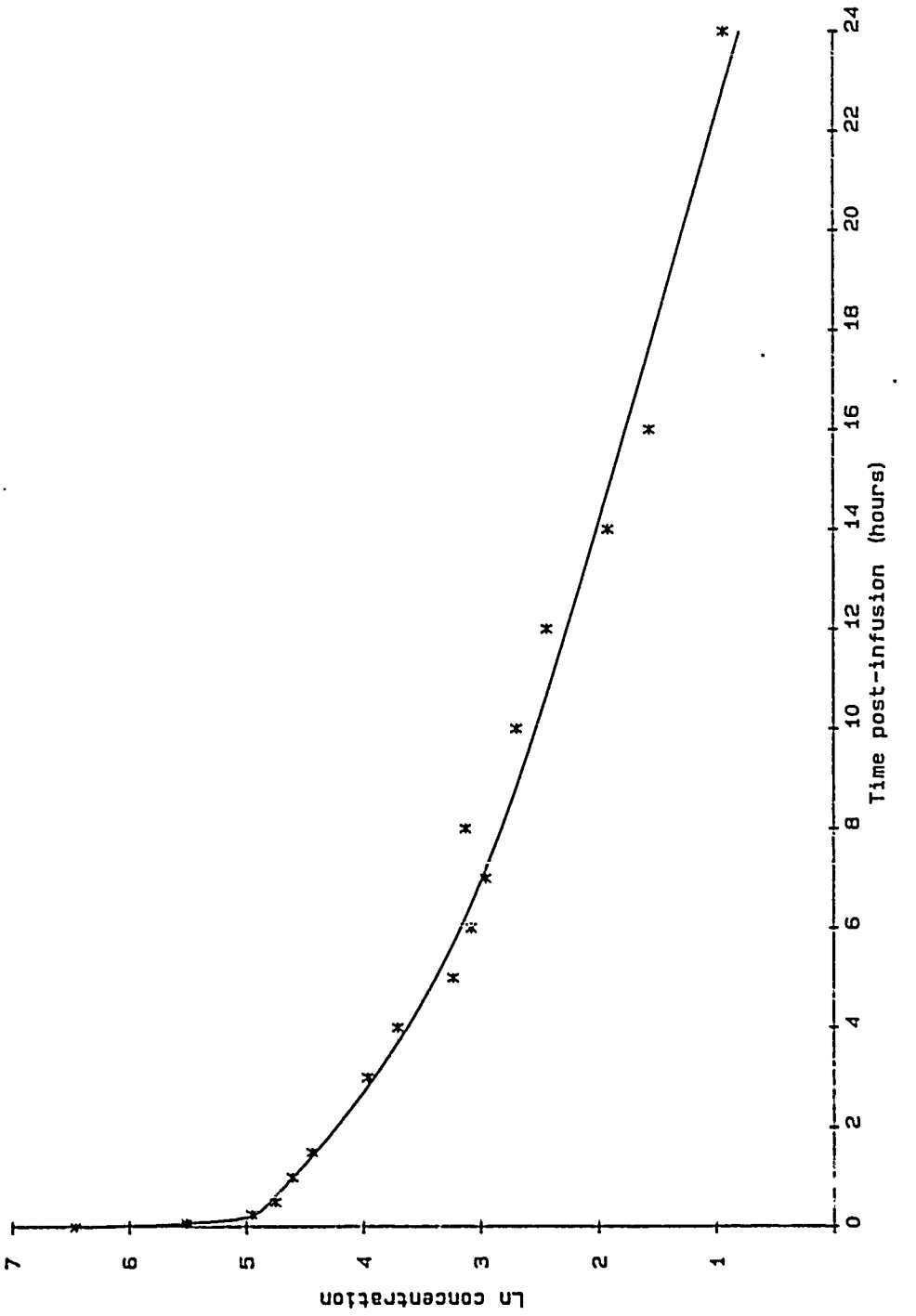


FIGURE 5

Measured plasma concentrations of pyridostigmine base (* - *) and concentrations calculated from a tri-exponential equation (solid line) fitted by non-linear regression after single intravenous infusion of 6.94 mg during 0.25 hours

Animal 4

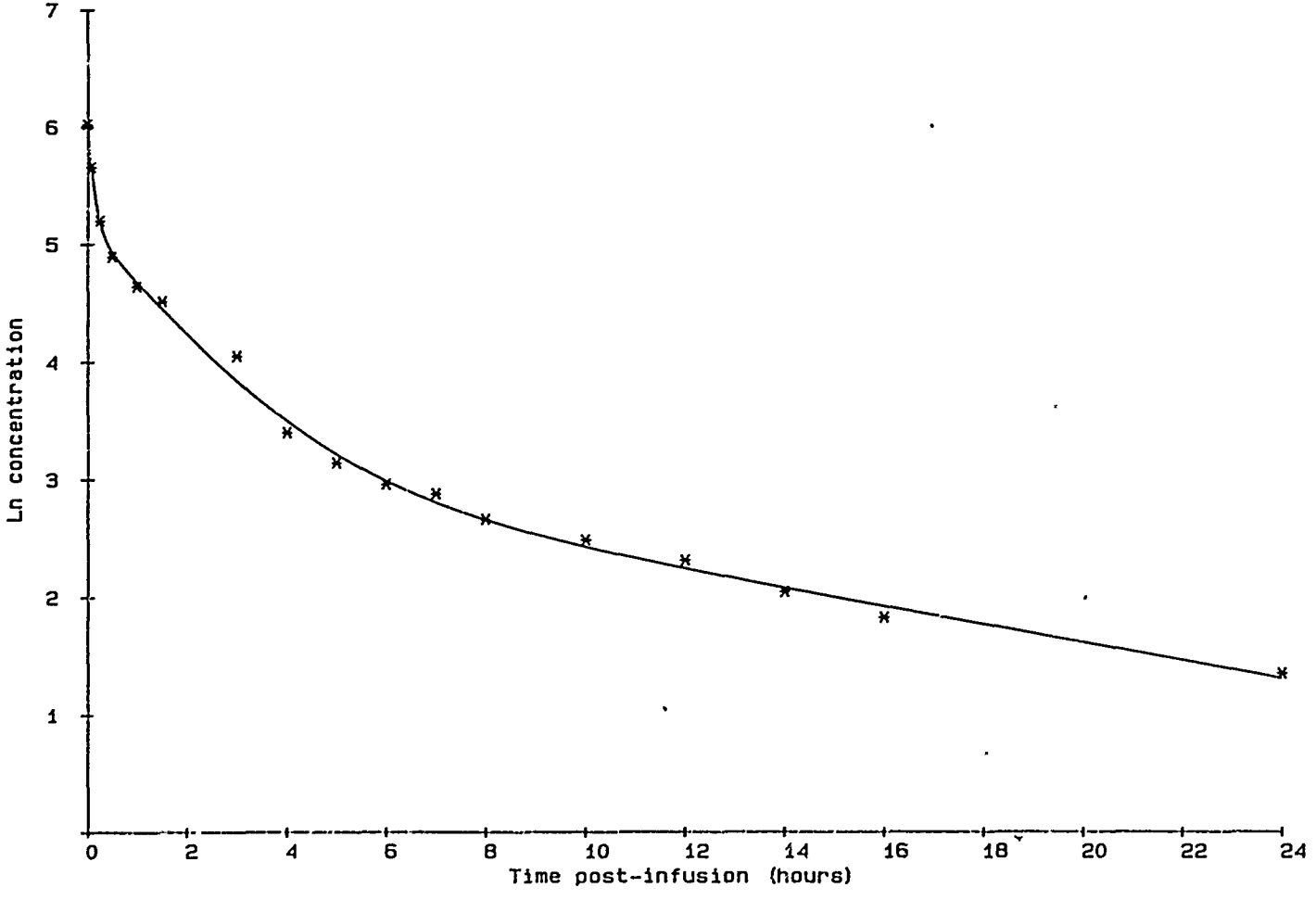


FIGURE 6

Measured plasma concentrations of pyridostigmine base (* - *) and concentrations calculated from a tri-exponential equation (solid line) fitted by non-linear regression after single intravenous infusion of 6.94 mg during 0.25 hours

Animal 5

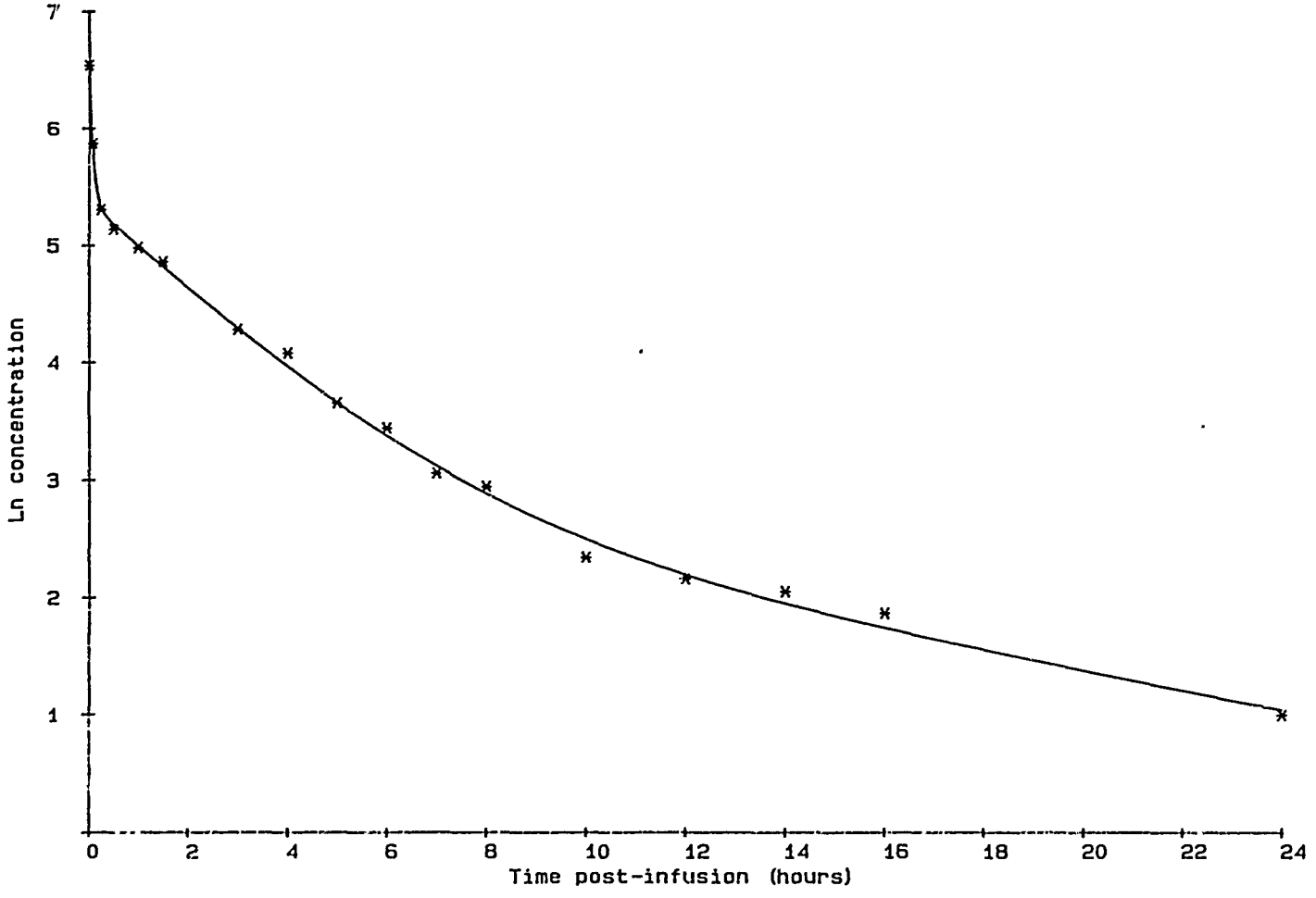


FIGURE 7

Measured plasma concentrations of pyridostigmine base (* - *) and concentrations calculated from a tri-exponential equation (solid line) fitted by non-linear regression after single intravenous infusion of 6.94 mg during 0.25 hours

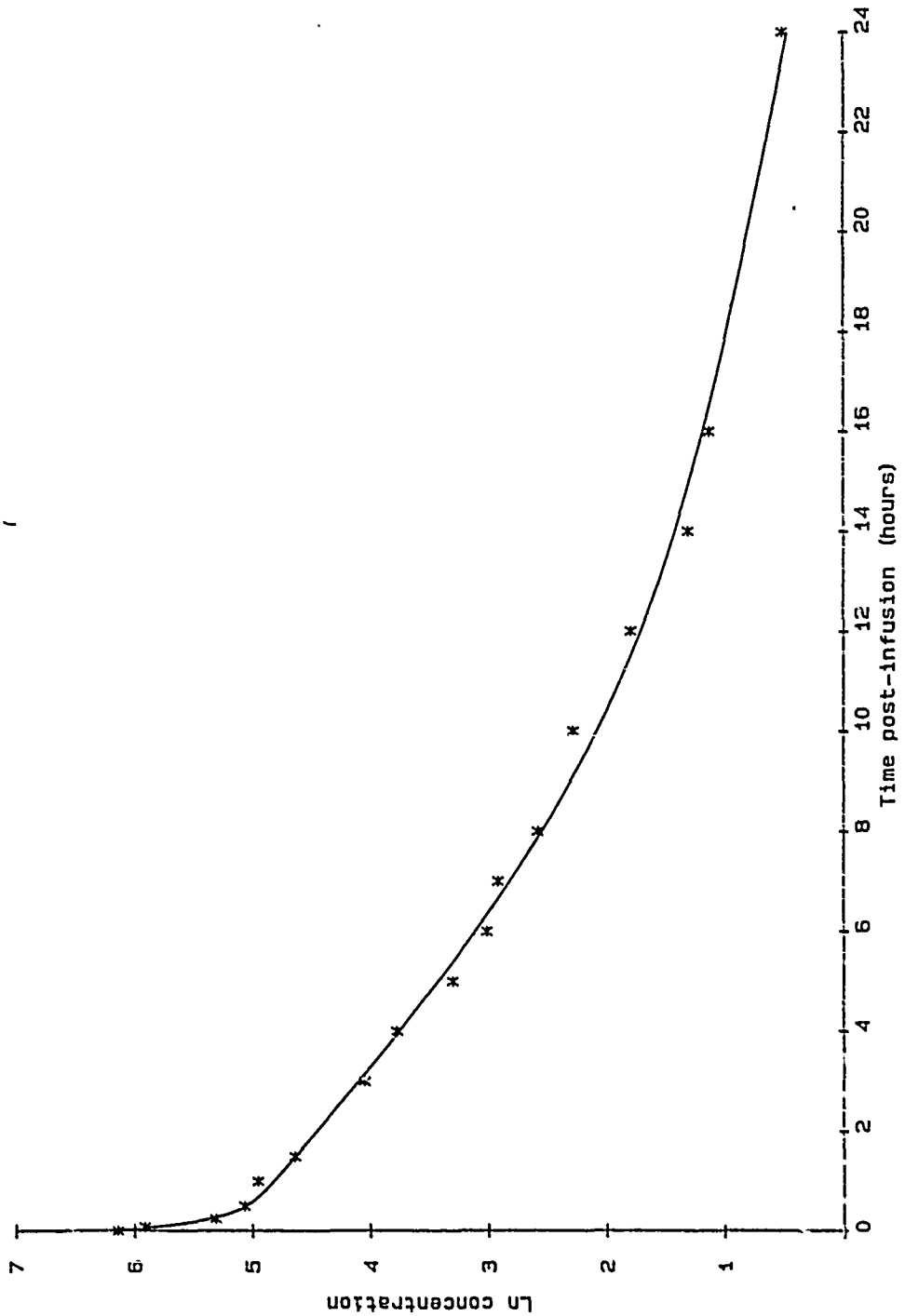


FIGURE 8

Mean calculated rates of drug transfer from ("elimination"; o-o) and to ("distribution"; ●-●) the sampling compartment after (transformation to)bolus intravenous doses of 6.94 mg (10 mg as the bromide salt) to dogs.
Semi-logarithmic scale

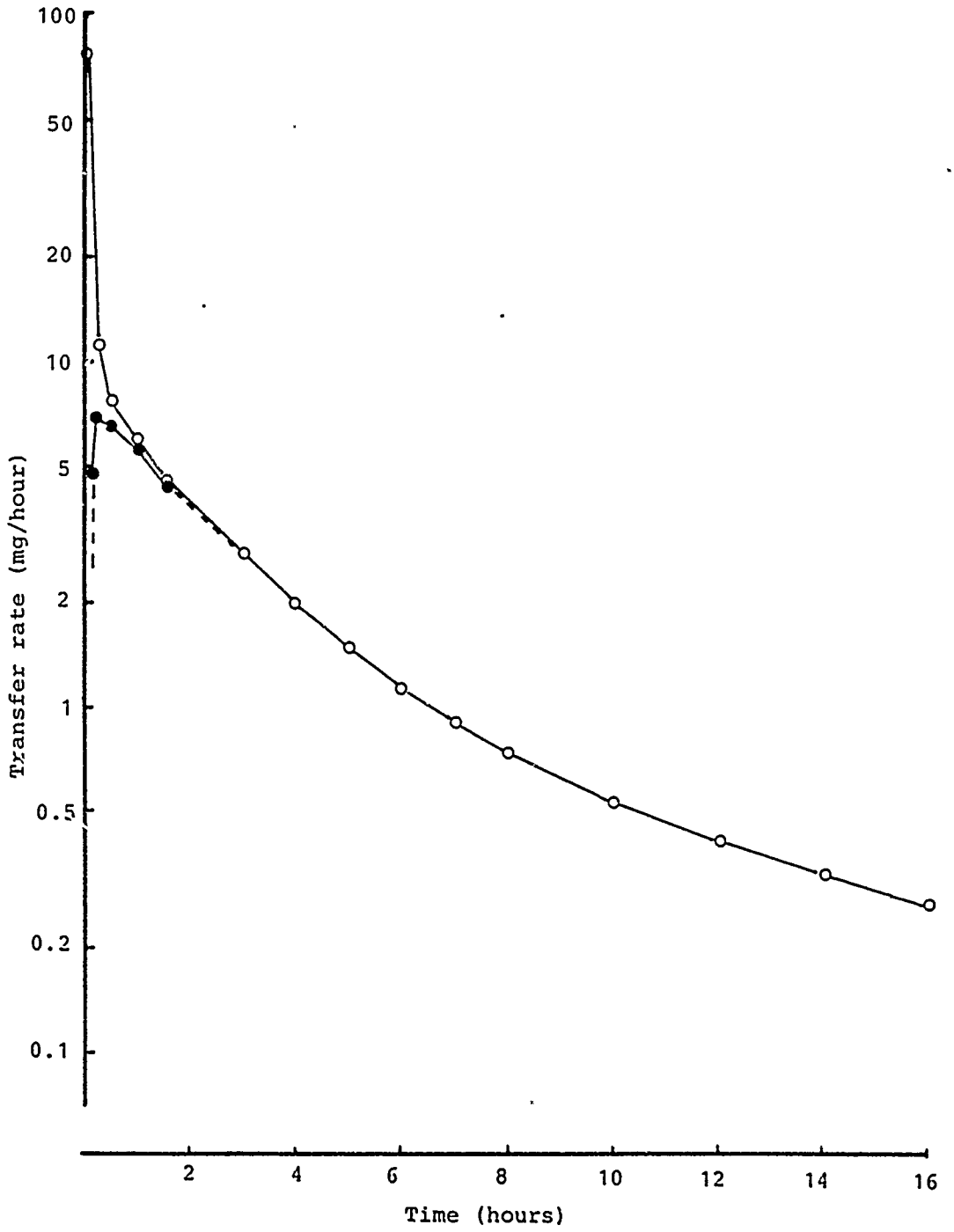
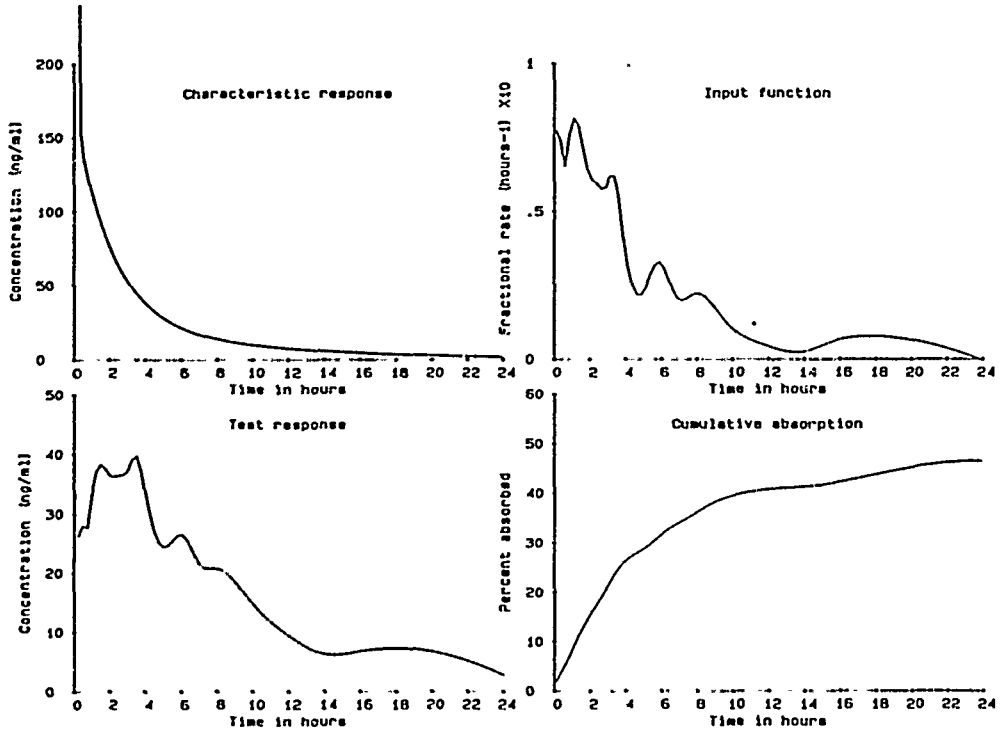


FIGURE 9[a]

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in a syrup) to dogs

Animal 1



[a] On Figures 9 through 20, the "characteristic response" is a representation of plasma drug concentrations calculated from tri-exponential equations fitted to the measured post-infusion data and transformed to bolus dose conditions (Table 9); the "test response" is a representation of plasma drug concentrations calculated from spline function fits (see p.7) to the measured data after oral doses of the syrup (Figures 9-14) and tablets (Figures 14-20); the "input function" is a representation of the instantaneous input rate of drug into the systemic plasma after the oral doses (Tables 17 & 18); the "cumulation absorption" is the cumulative percent dose available to the systemic plasma after the oral doses obtained by integration of the input function and summation (Tables 17 & 18)

FIGURE 10

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in a syrup) to dogs

Animal 2

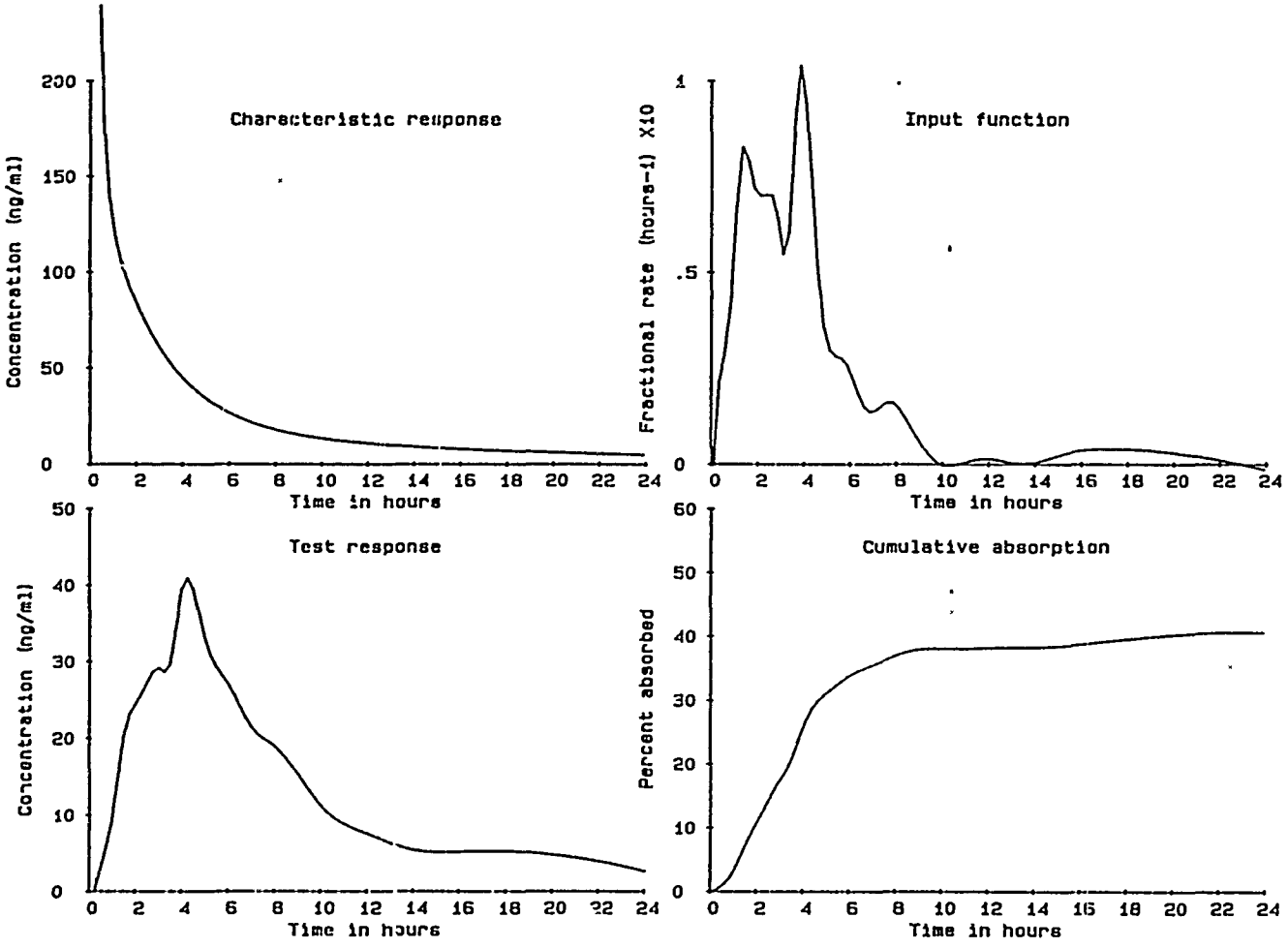


FIGURE 11

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in a syrup) to dogs

Animal 3

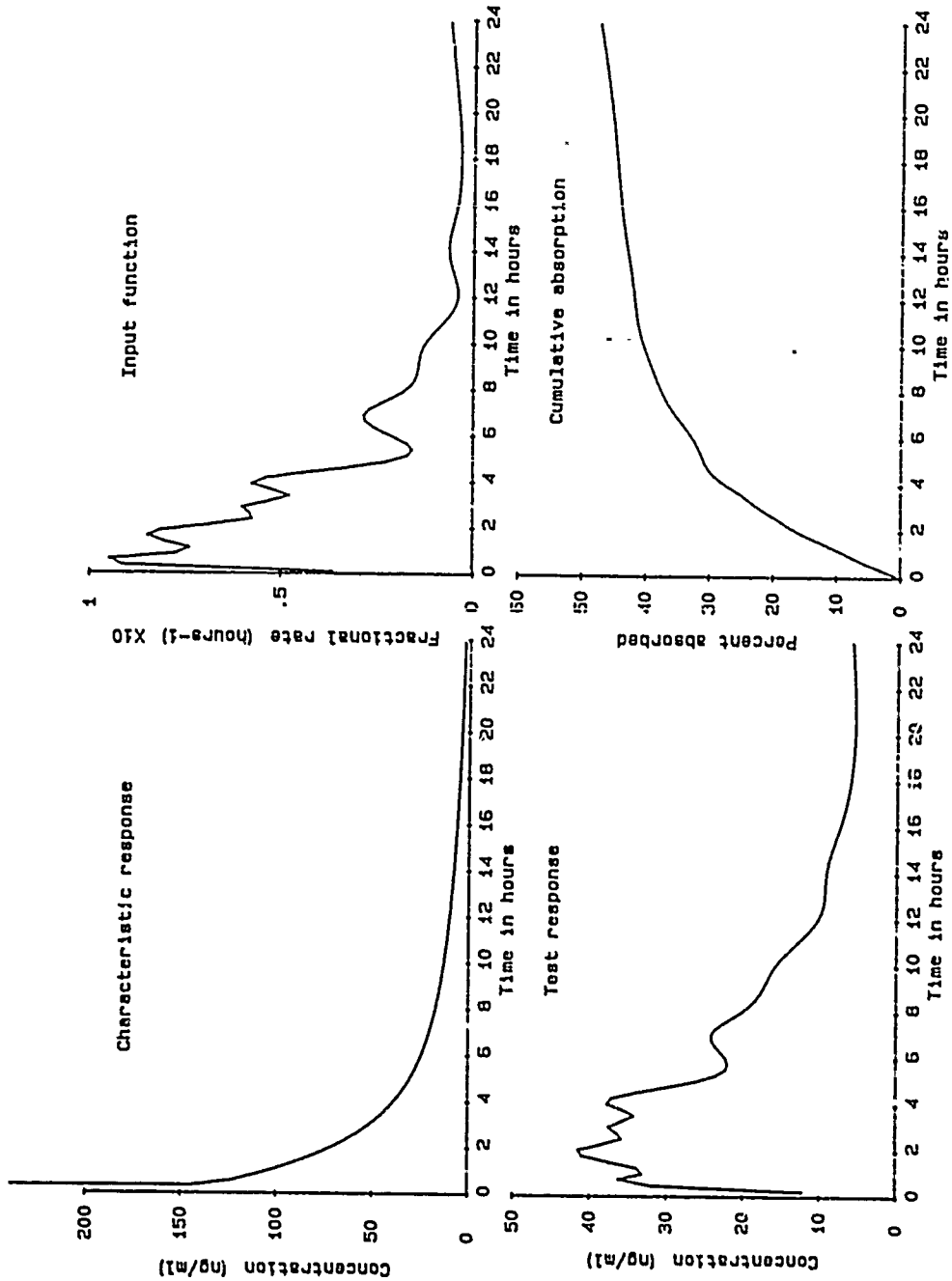


FIGURE 12

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in a syrup) to dogs

Animal 4

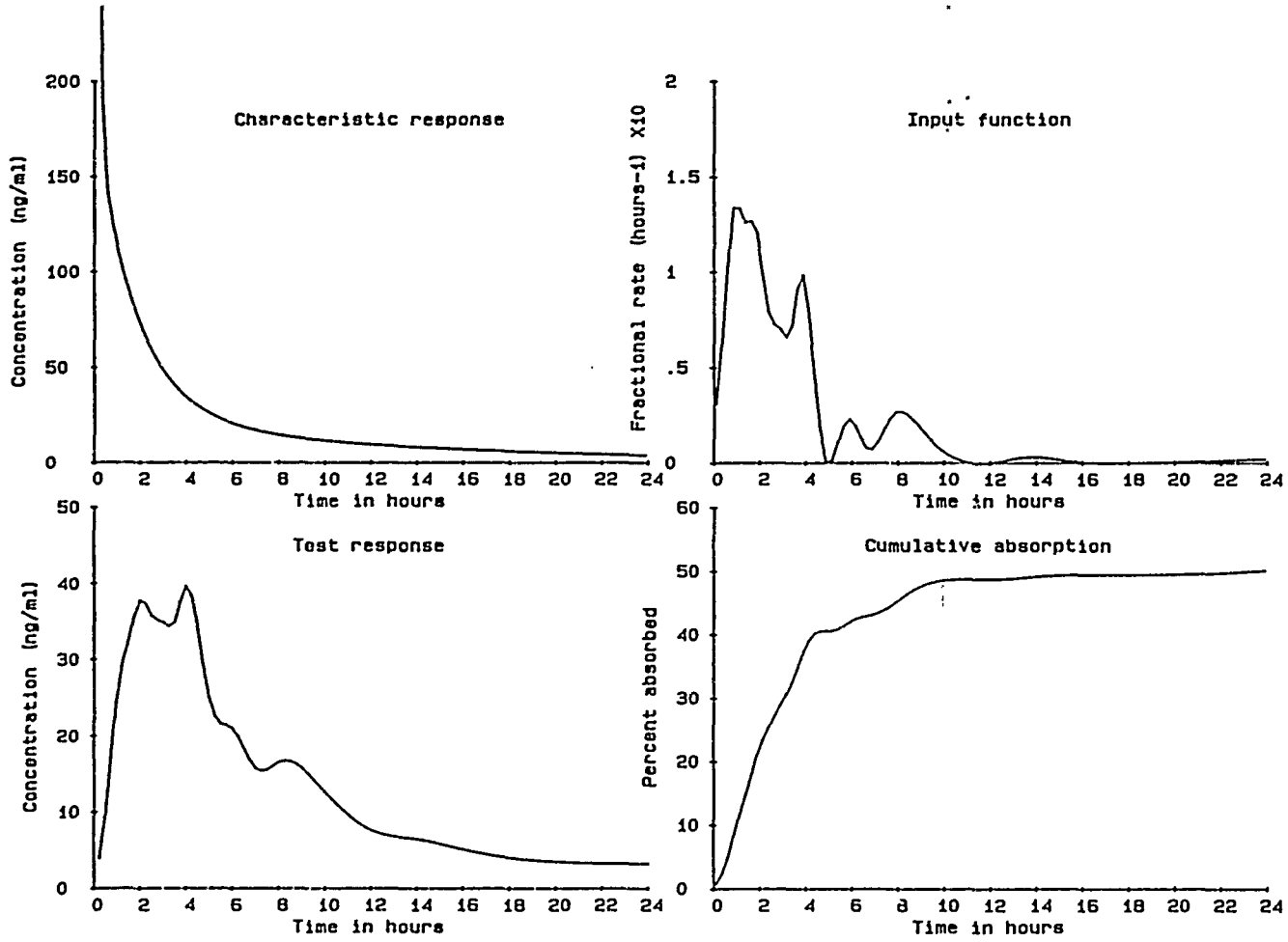


FIGURE 13

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in a syrup) to dogs

Animal 5

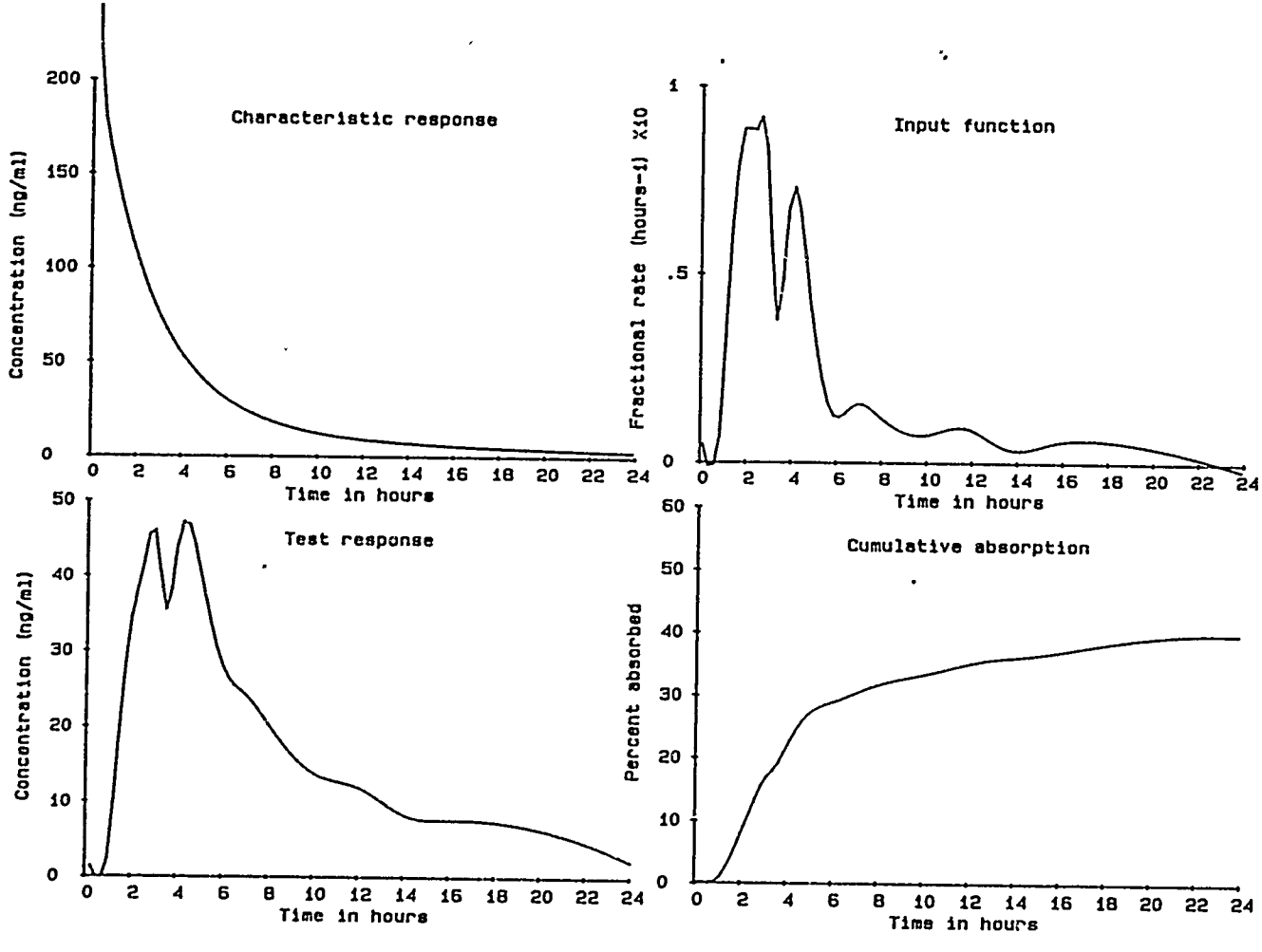


FIGURE 14

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in a syrup) to dogs

Animal 6

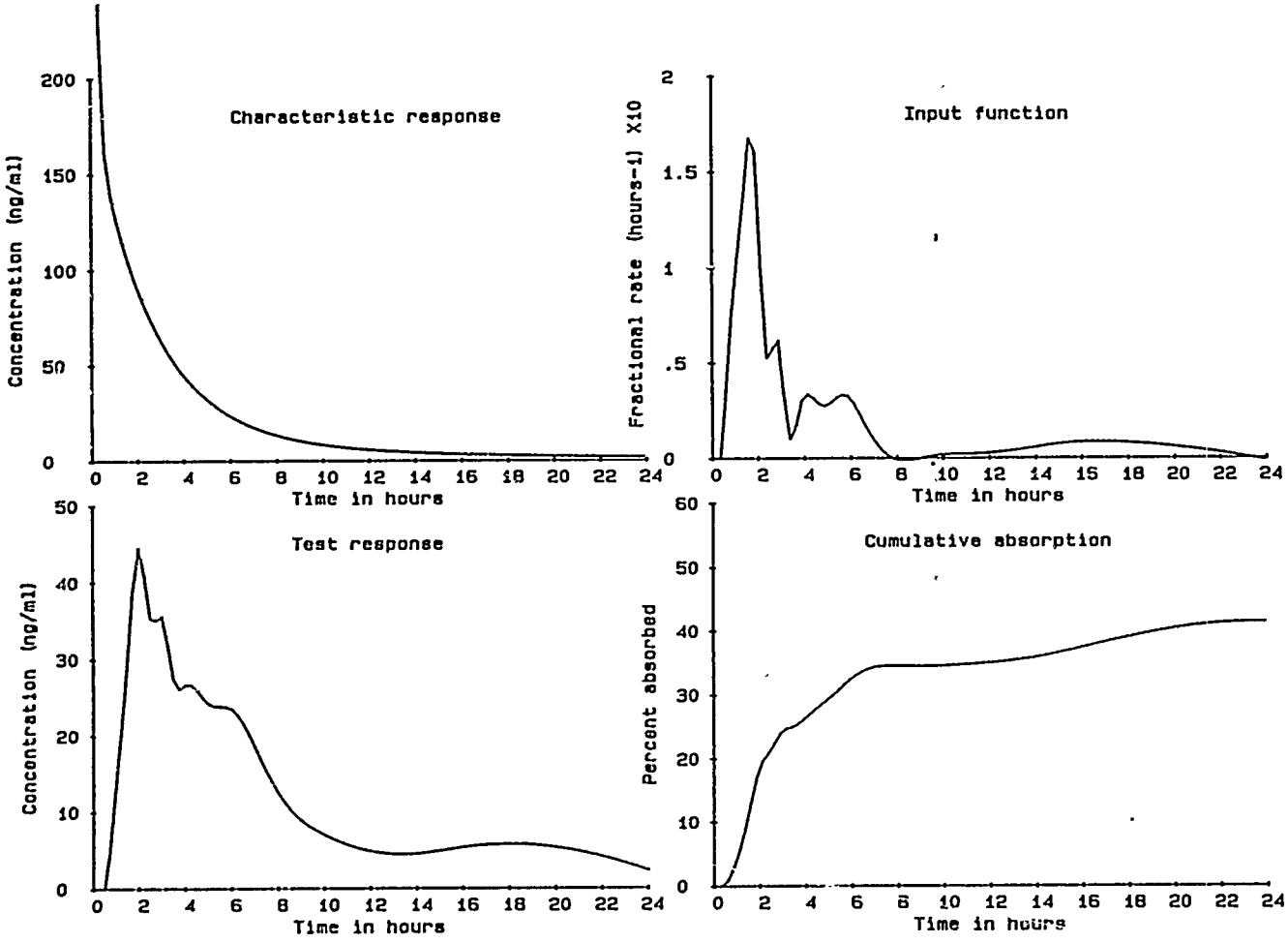


FIGURE 15

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in an extended-release tablet) to dogs

Animal 1

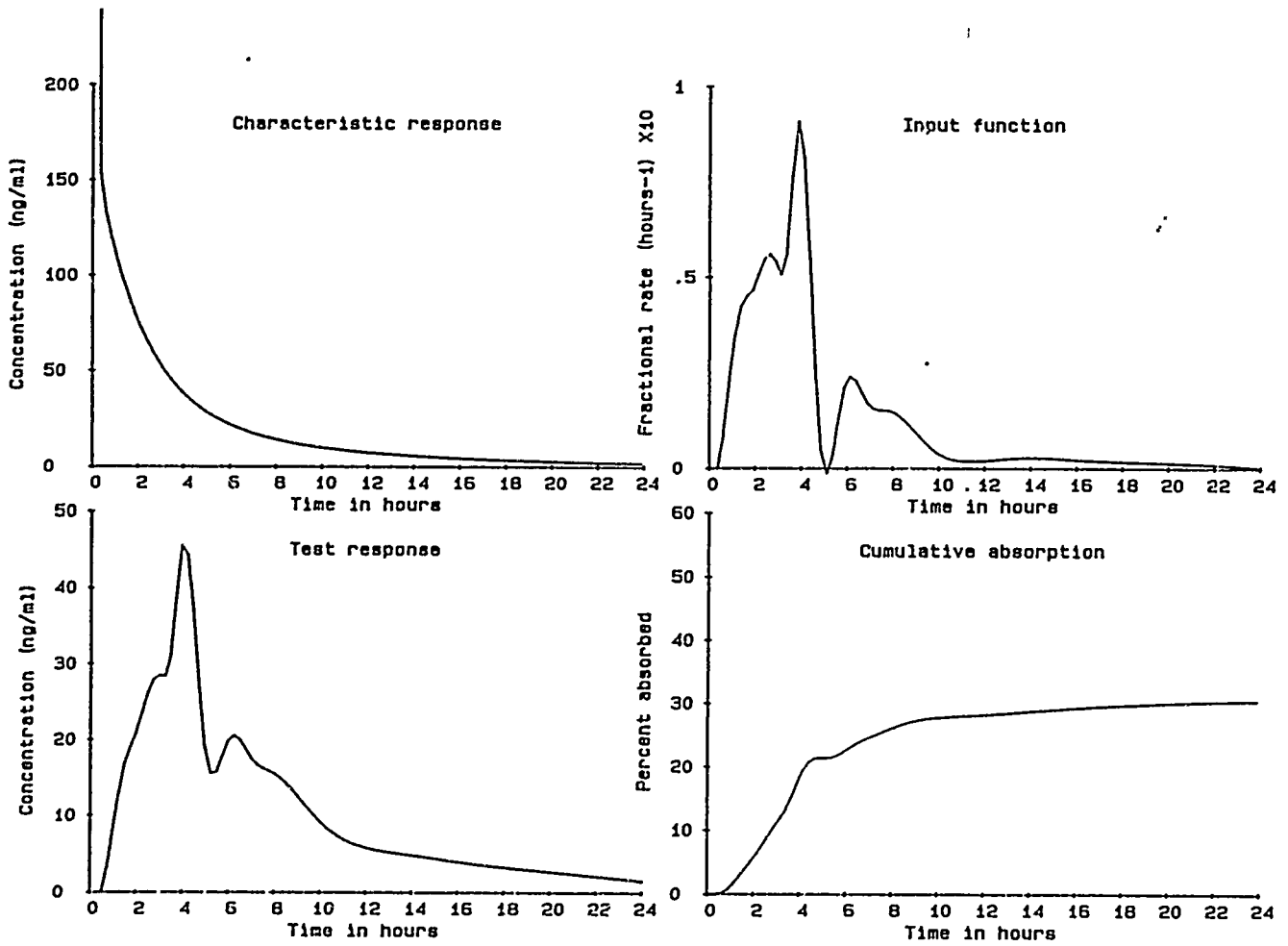


FIGURE 16

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in an extended-release tablet) to dogs

Animal 2

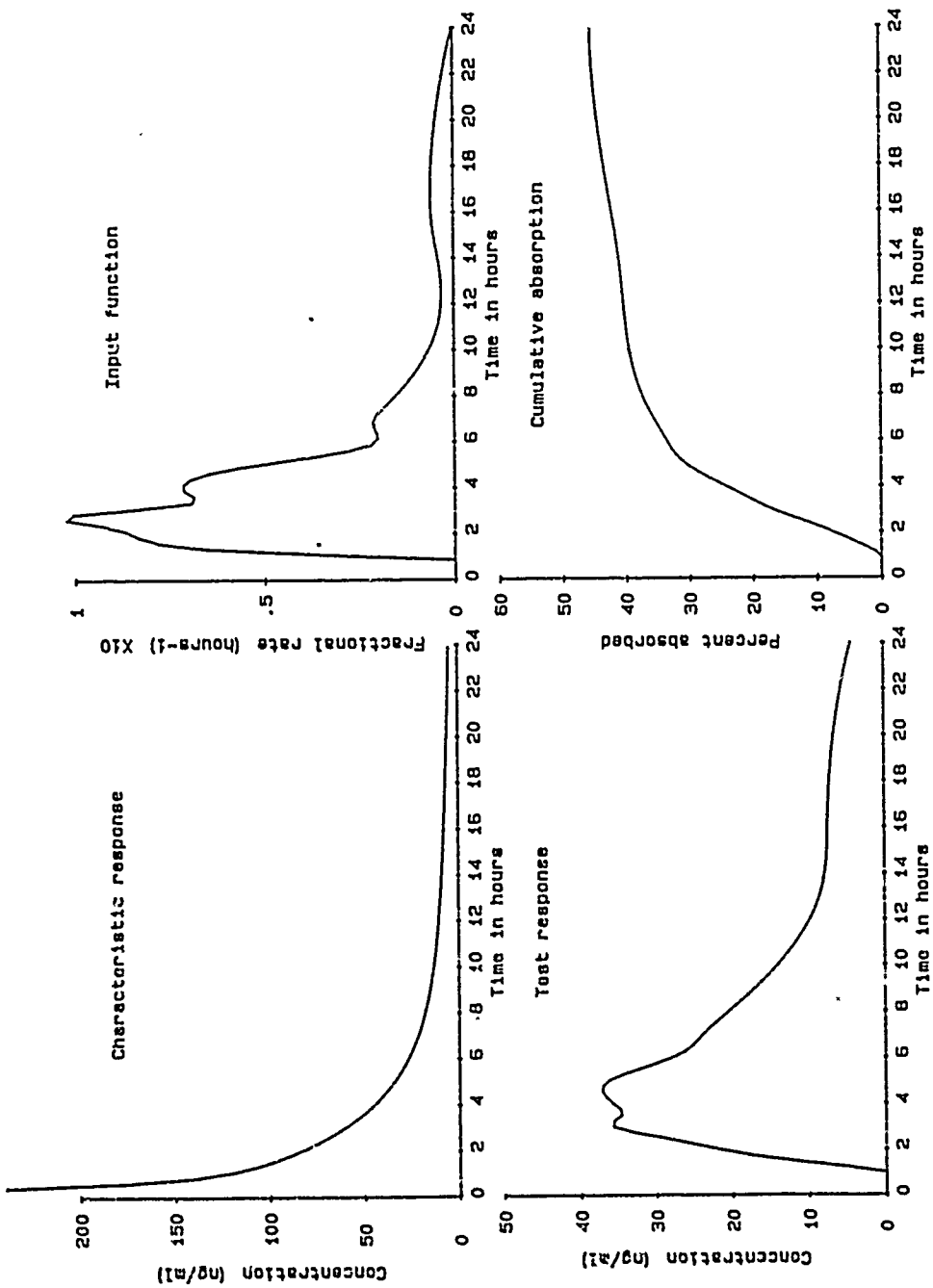


FIGURE 17

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in an extended-release tablet) to dogs

Animal 3

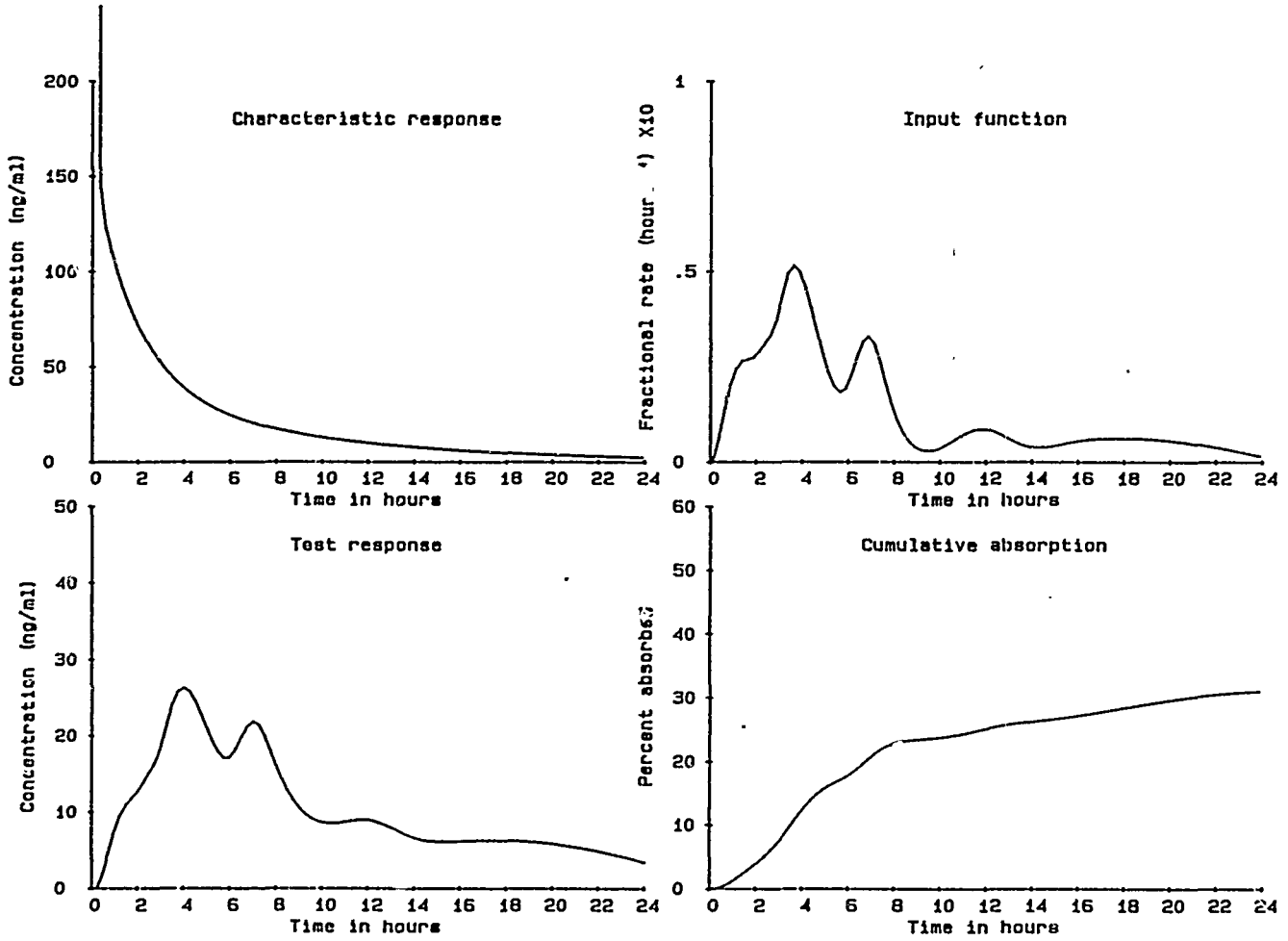


FIGURE 18

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in an extended-release tablet) to dogs

Animal 4

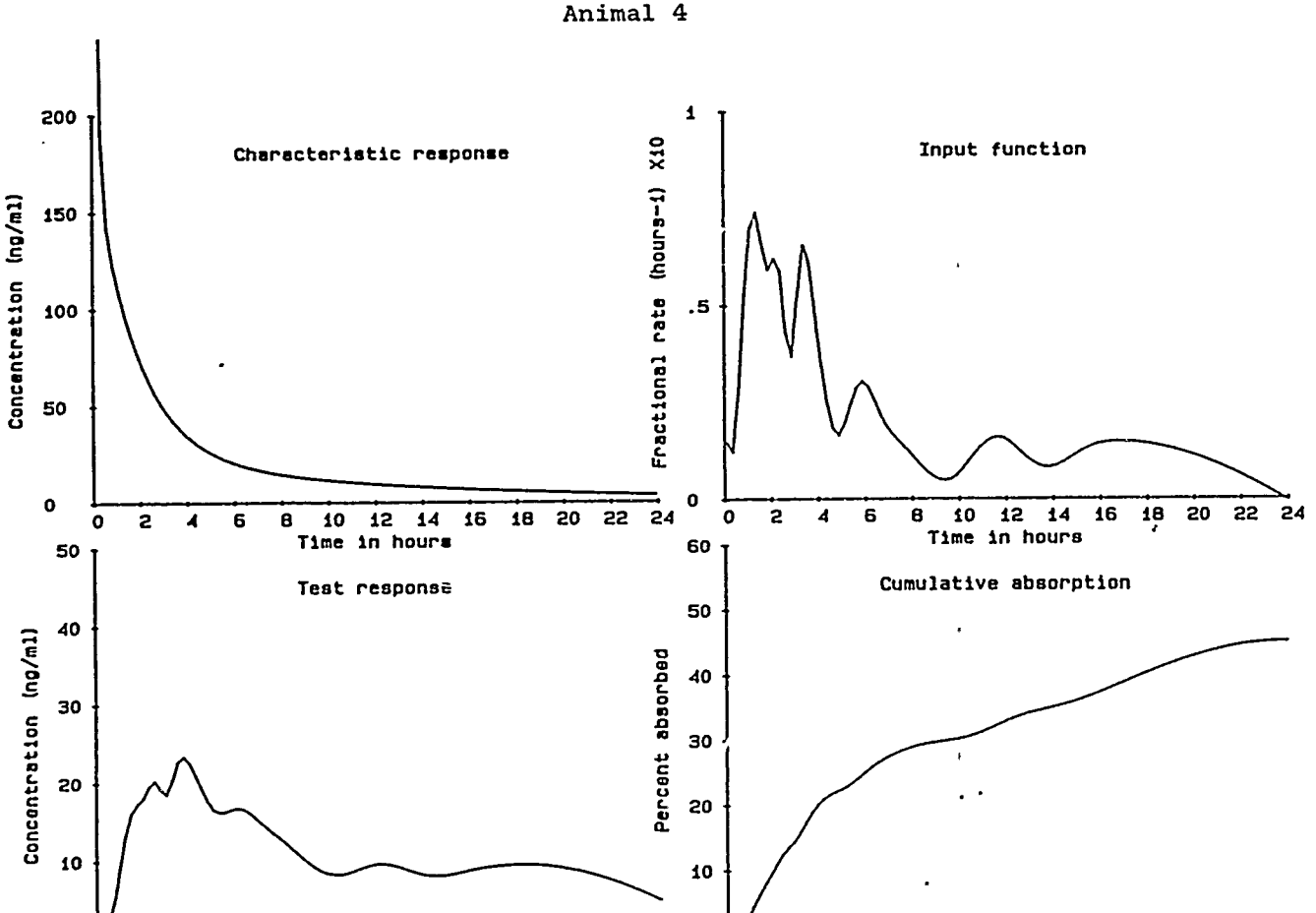


FIGURE 19

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in an extended-release tablet) to dogs

Animal 5

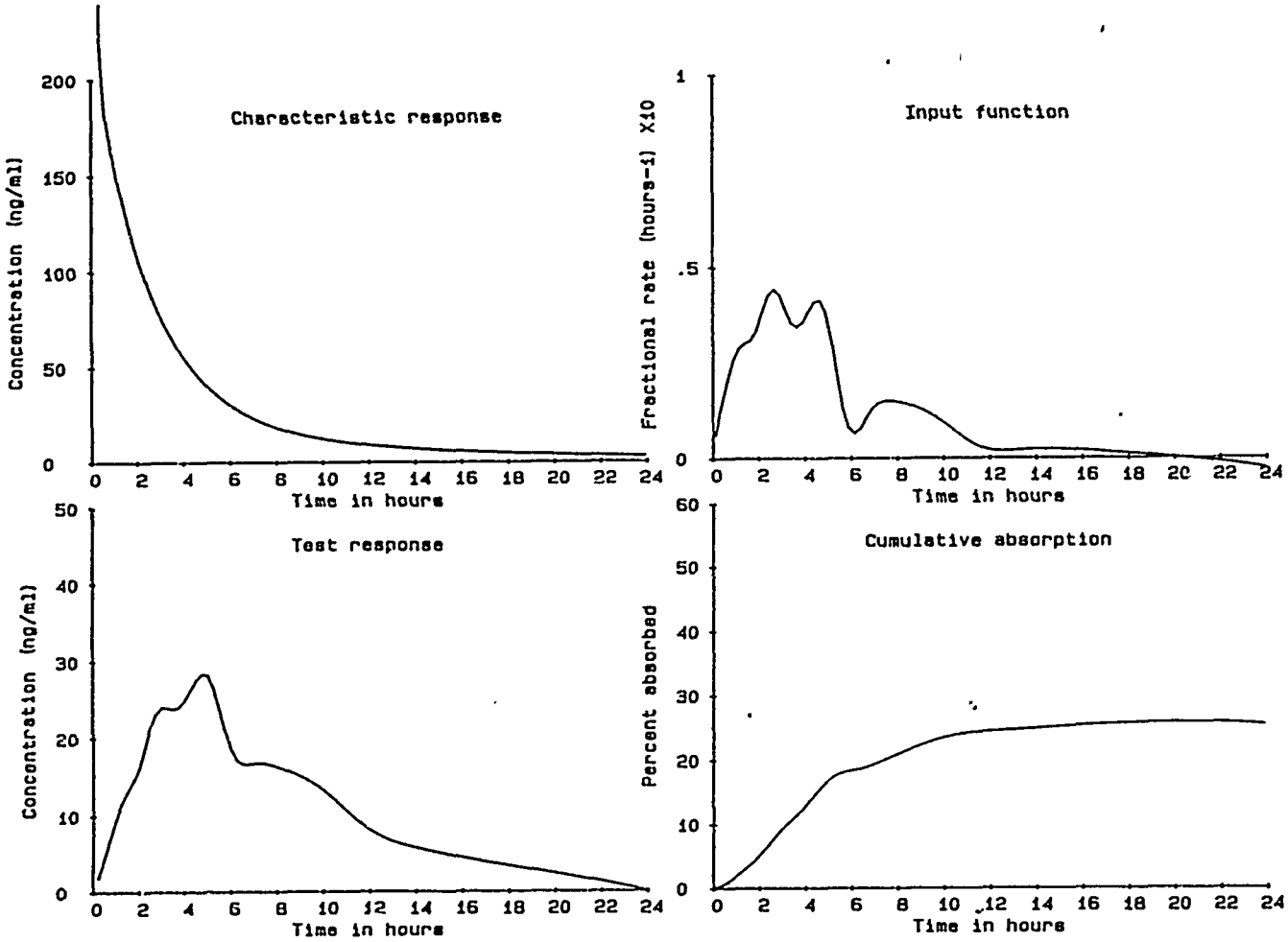


FIGURE 20

Input functions and cumulative absorption (availability) of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt in an extended-release tablet) to dogs

Animal 6

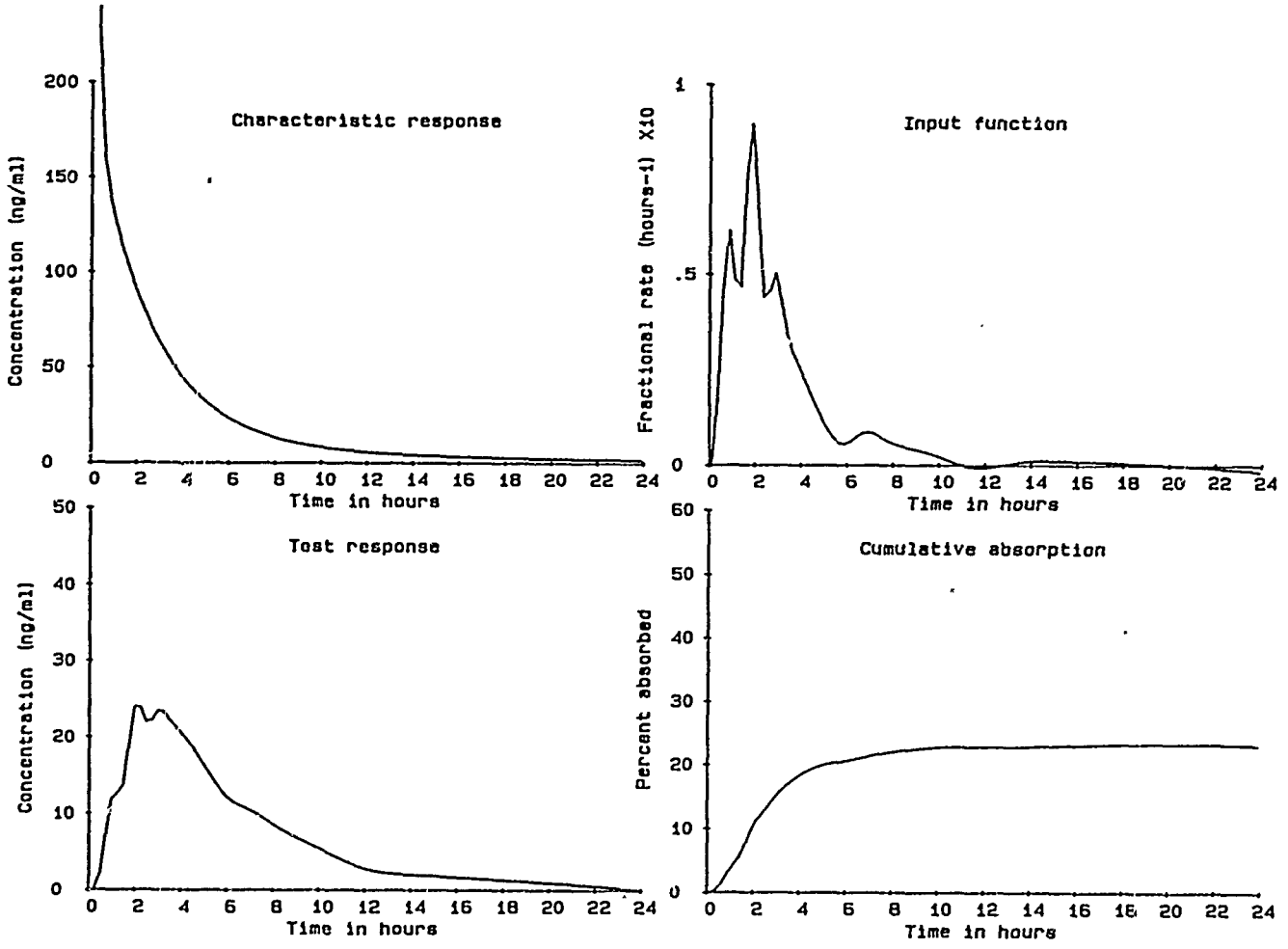
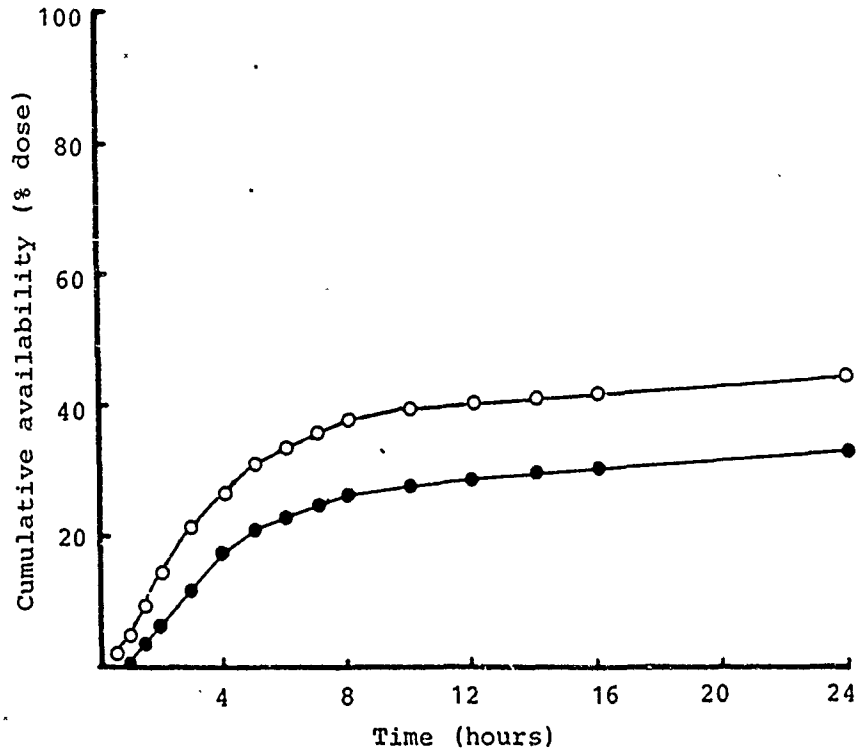


FIGURE 21

Mean cumulative systemic availability of pyridostigmine after single oral doses of 6.94 mg (10 mg of the bromide salt) in a syrup (o-o) and an extended-release tablet (●-●)



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